

Bio-Tetrarchy

How America Can Win the Biotech Revolution

Realistic US Reforms Based on International Comparison

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I. The Coming Biotech Revolution

Humanity is on the precipice of a revolution in biotechnology. AI-based genome analysis, bespoke gene therapy, and other technologies could unlock a new epoch in the war against disease. Four innovative nations stand at the threshold of this revolution. America, China, Japan, and Australia increasingly form a quadripolar world of competition and capital migration in biotech—a bio-tetrarchy.

America is, in general, still in the lead. Yet America also suffers from a unique weakness: a rigid system of universal, regulator-gatekept premarket approval based on multi-phase trials. Other nations, feeling the pull of the coming wave in biotech, have adopted increasingly flexible regulatory mechanisms to accommodate emerging therapies and drive innovation. America, too, must prioritize reforming its regulatory framework or be left behind.

Baby KJ Muldoon received his first personalized gene-editing treatment in February 2025. When publicly reported in May, his life-saving treatment was touted as a success of the American regulatory system.^[1] Yet the FDA itself admits that it has no commercially scalable pathway for this kind of individualized treatment. In November 2025, the FDA’s Martin Makary and Vinay Prasad acknowledged that—when it comes to bespoke treatments like Muldoon’s—“current regulations are onerous and unnecessarily demanding, provide unclear patient protection, and stifle innovation.”^[2]

The problem is not simply that the FDA paradigm produces inefficiency. The US system also lacks any pathway—even in principle—to truly accommodate the most promising frontier therapies. The American biologics framework, consisting of World War II-era statutes wrapped in decades of regulation, was simply not designed for individualized therapies. As the Christian Gospels say, “no one puts new wine into old wineskins.”^[3]

In contrast, China has already built a functioning and scalable legal framework for bespoke biologics. When the relevant technological breakthroughs arrive, China is poised to wholly overtake the US in biotechnology—just as it already has in open-source AI models, shipbuilding capacity, and other critical areas.

While many Americans recognize that the regulatory system needs significant reform, few legal minds—and even fewer biotech innovators—have attempted to pinpoint the fundamental problems with the FDA paradigm and put forward realistic reforms.^[4] This paper proposes to synthesize the key policy lessons of the bio-tetrarchy, distill them into systemic yet achievable policy proposals, and resolve the quadripolar order in global biotech into a new era of clear US dominance.

II. Basic Problems with the American System



The United States, China, Australia and Japan are the four great powers of biotechnology. Although South Korea, Singapore, and the United Kingdom warrant honorable mention as biotech innovators, ^[5] frontier biotech—particularly when it comes to pro-innovation policy—is now quadripolar.

Though America remains the world’s overall biotech leader, China threatens to outpace the US across all metrics. Previously a biotech backwater, China now surpasses the US, Europe, and Japan in new drug approvals^[6] and is the single largest source of novel drug candidates entering human trials. China’s share of Phase 1 trials passed America’s in 2021.^[7]

China is also a trailblazer in first-in-human clinical translation. It has quietly attracted American medical tourists since 2003^[8]—when it approved the world’s first gene therapy—and conducted the world’s first human CRISPR trial in 2016. China also approves new studies faster than the United States^[9] and, thanks to both regulatory efficiency and easier patient recruitment, conducts trials at as little as a third of the cost.^[10]

While China vies with the US for the top spot in biotechnology, Australia has carved out a unique role for itself at the crossroads of both powers. Both America and China look to Australia for different kinds of support.

For American companies, Australia offers a system substantively similar to China's without the political contamination and legal risk of doing business in China itself. To Chinese companies, on the other hand, Australia offers a structurally familiar legal system that will be politically acceptable to the FDA^[11] and thereby facilitate access to American patients.^[12] In this way, Australia has become a kind of Silk Road between Western and Eastern forms of innovation in policy and biotechnology.

Australia has leveraged this position to become a worldwide leader in Phase 1 trials. It now ranks first in the world for the initiation of commercially sponsored clinical trials per capita and third globally for the total number of Phase 1 trials initiated.^[13]

Meanwhile, American companies rely on Japan for a different sort of policy arbitrage. While Australia is seen as the best country in the world for Phase 1 trials, government-sponsored coverage describes Japan's pathway to rapid commercialization and patient access as "widely seen as the fastest in the world."^[14] Japan has positioned itself as a global on-ramp to the market, with American biotech companies—including large pharmaceutical corporations like Pfizer^[15]—using the Japanese framework to sell therapies in Japan before they can treat patients in the United States.^[16] Japan also slightly eclipses China in biotechnology patents, coming in second behind the United States,^[17] and is usually ranked as a top-four jurisdiction for new drug approvals.^[18]

This paper contends that America's competition with China, as well as its growing reliance on Australia and Japan, is a self-imposed policy choice. To understand the successes of our peer nations in biotechnology, it also compares America's legal regime to each of its competitors and draws on conversations with innovators familiar with all four systems.

All members of the bio-tetrarchy share certain broad norms: the US, China, and Japan are all full regulatory members of the ICH, or "International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use," while Australia is an ICH observer.^[19] Yet the United States' system has a unique combination of self-limiting features.

The American framework is sponsor-driven, universally regulator-centered, and regulator-gatekept—utilizing "*ex ante*," or premarket, approval based on a system of multi-phase trials. This system is also uniformly compulsory in the sense that, alone among the bio-tetrarchy, it essentially permits no other scalable routes to commercialization for drugs and biologics. We can call this uniquely American combination of features the "FDA paradigm." This paper will compare the FDA paradigm with its major competitors in detail and consider some of its specific implications for frontier technologies.

First, it's worth considering some broad, distinctive features of the FDA system and the way many Americans conceptualize it. Next to China, Japan, or Australia, certain basic problems with America's system stand out.

A. The overbreadth of “drug” and “biologic”

In the United States, the legal categories of “drug” and “biologic” are breathtakingly broad, theoretically encompassing any physical article used in treating patients other than a medical device. As a result, the shadow of US regulatory authority—not to mention the three-phase trial process—covers a broader spectrum of medical practice than in any peer nation. The upshot is that the FDA paradigm chills, obstructs, or *de facto* prohibits therapies that enjoy streamlined pathways overseas. This overbreadth has its origins in the federal statutes creating the FDA system.

While an entity called the “Food and Drug Administration” has existed since 1930, it was initially focused on licensing and mislabeling. It inherited this role from the earlier Bureau of Chemistry—created as part of Theodore Roosevelt’s “Square Deal” program.

The current FDA paradigm did not begin to germinate until 1938, when Franklin Roosevelt signed the Federal Food, Drug, and Cosmetic Act (“FD&C Act”). The FD&C Act was passed in response to the 1937 “Massengill massacre”^[20] in which Tennessee pharmaceutical company S.E. Massengill poisoned children with an untested toxic solvent in “elixir sulfanilamide,” killing over a hundred people in fifteen states.^[21] Amazingly, Massengill had not subjected the solvent, diethylene glycol, to testing of any kind—not even on rats—before shipping it commercially across the United States. Had Massengill simply conducted basic animal testing on the solvent, the animals would have died.

The FD&C Act required that any drug be subject to regulator-gatekept premarket testing, albeit only for safety and without the current three-phase trial system. The FD&C Act defines a “drug” as any article “intended to affect the structure or any function of the body.”^[22] Despite this sweeping definition, hearings and committee reports at the time are full of assurances that the FD&C Act would be limited in scope and would not interfere with medical practice.^[23] In response to the concerns of doctors, Senator Royal Copeland—the FD&C Act’s author and prime sponsor—continually assured them that “the medical practitioner shall not be interfered with in his practice.”^[24]

In 1944, FDR also signed the Public Health Service Act (“PHS Act”), establishing similar regulatory oversight of biologics. The PHS Act defines a biologic in similarly expansive terms: a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative ... or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings.”^[25] Initially, biologics were overseen by the National Institutes of Health rather than the FDA.

Many familiar aspects of the FDA paradigm originated only much later as the FDA continued to grow in size and power. Mandatory efficacy testing was first required by a 1962 statute, while the “phase” system was not formalized in any regulation until 1963.^[26]

The omnipotence of the terms “drug” and “biologic” has been compounded by judicial opinions disregarding the undisputed original intent of the FD&C Act and PHS Act. The leading case testing the limits of the terms “drug” and “biologic” is the D.C. Circuit’s 2014 decision in *United States v. Regenerative Sciences, LLC*.

In *Regenerative*, the D.C. Circuit upheld a district court injunction against Regenerative Sciences, a provider of autologous stem cell therapy. Regenerative Sciences had taken the position that its therapeutic techniques were a form of medical practice and were therefore not subject to the cost-prohibitive FDA paradigm of premarket approval and multi-phase testing. The court held that a patient’s own mesenchymal stem cells (“MSCs”) qualified as both a “drug” and “biologic” for purposes of federal regulation simply because Regenerative Sciences cultured and treated them with doxycycline—an antibiotic—to prevent contamination.^[27]

Regenerative Sciences urged that stem cells from a patient’s own body cannot be a drug or biologic under applicable federal law.^[28] The D.C. Circuit strained to avoid this argument. It conspicuously avoided using the term “stem cells” to describe MSCs. Instead, because the MSCs had been cultured and treated with doxycycline, the court characterized the stem cells as a “resulting mixture (the Mixture).” It then described the MSCs as “the Mixture” throughout the remainder of the opinion.^[29]

The company also emphasized historical evidence showing that “the [FD&C Act] was not intended to regulate the practice of medicine”^[30] and urged the court to read the FD&C Act and PHS Act in light of the states’ traditional role in regulating medical practice. The court responded that, “[n]otwithstanding appellants’ attempt to characterize this case as an effort by the FDA to ‘restrict[] the use of an autologous stem cell *procedure*,’... the focus of the FDA’s regulation is the *Mixture*.”^[31]

No one seriously denies that a literal reading of the federal “drug” and “biologic” definitions encompasses autologous stem cell therapy. It is true that these definitions encompass essentially any physical article used in medical practice other than a medical device. Still, it’s striking that the *Regenerative Sciences* Court granted the appellants’ key premise—that the FD&C Act was never intended to regulate medical practice—but upheld FDA authority anyway, reasoning that the FDA was not regulating an autologous stem cell procedure but merely “the *Mixture*” itself.^[32] This reasoning essentially places any physical article produced by or used in a medical procedure within the FDA paradigm.^[33]

One implication of *Regenerative Sciences* is that the FDA could clearly regulate a broad range of procedures that it has traditionally regarded as medical practice. For example, the FDA could regulate *in vitro* fertilization on the grounds that it is regulating the IVF embryo. The embryo produced by IVF—which, like autologous stem cells, is cultured in media—equally satisfies a literal textual reading of “drug” or “biologic” under the FD&C Act or PHS Act. The embryo is an article “intended to affect the structure or any function of the body,”^[34] and is a biological product “applicable to the... treatment, or cure of a disease or condition [infertility] of human beings.”^[35]

The *Regenerative Sciences* Court went on to emphasize the constitutionality of the FDA paradigm by citing *Wickard v. Filburn*,^[36] which stretched the Constitution’s Interstate Commerce Clause to give the federal government power over most aspects of daily life.^[37] This is poetic, since *Regenerative Sciences* is itself an analogue of *Wickard*. As *Wickard* expanded the Interstate Commerce Clause to give the federal government *de facto* plenary power, a literal but anachronistic reading of the FD&C Act and PHS Act has given the FDA a backdoor into the wholesale regulation of medicine—nullifying the traditional prerogatives of the states and medical boards. In American law, any enumerated powers eventually metamorphose into plenary powers.

A few therapies which meet the definition of “drug” and “biologic” are nonetheless still regulated only by licensing boards, state officials, and private institutions. IVF, as well as certain peptides and other bulk drug substances, are examples. Yet this is largely thanks to regulatory grace and enforcement-discretion policies, not binding law. As far as Congress and the courts are concerned, the FDA is free to act as an omnipotent bureau of American medical practice.

Ironically, China has a comparatively less authoritarian framework, preserving a meaningful boundary between drugs and biologics, on the one hand, and medical practice on the other. This commonsense distinction directly facilitated China’s first-in-human CRISPR therapy, which China correctly views as a therapeutic technique—akin to gene surgery—requiring more flexible regulation than a standard biologic.

The COVID-19 challenge trial debacle

The problems with America’s sweeping categorization of nearly every physical article in medicine as a “drug” or “biologic” were sharply highlighted during the COVID-19 pandemic. In early 2020, American scientists led the campaign to conduct human “challenge trials,” in which healthy volunteers would be deliberately infected with COVID-19 to speed the development of a vaccine.^[38] By April 2020, the whole American scientific and political establishment was largely united behind the need for challenge trials; a bipartisan letter from members of Congress urged the FDA and HHS to consider taking all steps necessary to facilitate challenge trials. Nearly 25,000 people informally volunteered online.^[39]

Juris dictio n	Classification of challenge agent	Practical gate
Unite d State s	Biologic under PHS Act § 351; FD&C Act.	IND under 21 CFR Part 312, GMP manufacture, FDA safety/purity/potency review—plus ethics review. A <i>de facto</i> prohibition as applied to urgently needed trials.

Juris dictio n	Classification of challenge agent	Practical gate
Euro pean Unio n	A study solely of disease physiology using a challenge agent falls outside the EU Clinical Trials Regulation; a study investigating a medicinal product may fall within it.	For disease-physiology studies outside the Regulation, member states determine whether and how to regulate the study. ^[40] Trials of an investigational medicinal product remain subject to the Regulation's authorization requirements.
Unite d King dom	Challenge agent treated as a non-medicinal product and, in a medicinal-product trial, as a non-IMP.	Disease-model studies require ethics review but no MHRA clinical trial authorization (CTA), and the challenge agent receives no MHRA GMP certificate. Medicinal-product efficacy trials require a CTA, with the challenge agent assessed as a non-IMP.

Yet even elite consensus could not overcome the status quo bias and sheer inertia created by the FDA paradigm. By February 2021, the challenge-trials effort had been driven overseas to the United Kingdom after federal agencies failed to issue the necessary nonenforcement guidance.^[41]

It may seem odd that innovation should escape from the United States to the United Kingdom. The UK is not known for being particularly pro-innovation—and both countries have similar processes for ethical review. Yet American law has a distinctive weakness the UK does not: it bizarrely classifies the challenge pathogen itself as a “biologic.” The virus would therefore need to be the subject of an IND application, receive FDA approval, and be manufactured under Good Manufacturing Practice conditions—all in addition to ethical review. This is a *de facto* prohibition on any urgently needed challenge trial.

The UK treats a non-medicinal challenge agent as a research instrument rather than as an investigational medicinal product. A study solely modeling infection therefore does not require an MHRA clinical trial authorization—the UK counterpart of an IND—and the challenge agent does not receive an MHRA GMP certificate. UK classification therefore avoids a separate authorization gate and formal MHRA GMP certification for the challenge agent.^[42]

No powerful interest group seems to have consciously worked to stop US challenge trials. Unconscious emergent forces drove the research overseas. The FDA paradigm simply acted as a blind, categorical machine, grinding every advance in medicine into the same one-size-fits-all mold of regulator-centered, multi-phase premarket trials.

The system itself naturally leans towards obstructing innovation. Keeping these challenge trials in the United States would have required willpower, force, and perseverance.

B. Sponsor-driven and regulator-gatekept

A second basic problem with the FDA paradigm is that the approval process for drugs and biologics in the United States is uniformly *sponsor-driven and regulator-gatekept*. A private sponsor must maneuver a therapy through the regulatory process at the sponsor's ongoing expense. Meanwhile, only federal regulators can ever determine that a therapy has demonstrated sufficient safety and efficacy to reach patients at scale—or even that trials can begin at all.

In our peer nations in the bio-tetrarchy, many aspects of clinical trials are more *IRB-gatekept* than regulator-gatekept. Under Australia's now-renowned Clinical Trial Notification (“CTN”) system, the sponsor simply obtains approval from a private review board—a “Human Research Ethics Committee”—and then notifies the Therapeutic Goods Administration, Australia's version of the FDA, that it is beginning a trial. American biotech companies, accustomed to prostrating themselves before the vast edifice of the state, are often incredulous at CTN. “[American companies] often say to us, ‘Are you sure that's all we need to do?’” one Australian biotech consultant has said. “We are sure, and that is all you need to do,” she tells them.^[43]

China's system goes even further. China operates a system of Investigator-Initiated Trials (“IIT”) similar to the Australian CTN system in which a qualifying hospital and its IRB directly approve certain clinical trials.^[44] While not every Chinese trial is a candidate for an IIT, qualifying research in the IIT framework can proceed on institutional academic and ethical approval and filing with health authorities; later clinical translation requires a separate national approval. Although precise numbers are hard to come by, China likely conducts hundreds or thousands of IITs per year.^[45] In May 2026, reforms promulgated by China's State Council in September 2025 took effect, standardizing research filing and establishing a distinct approval pathway for clinical translation.^[46] Japan has a similar—if less well-developed and less extensive—pathway, with state-certified but private review boards able to authorize treatments for large categories of human cellular therapies.^[47]

Separately, China's four “green channel” pathways—first codified in 2020—give regulators mechanisms for targeted acceleration, staged evidence review, and intensified guidance, although sponsors still apply for these procedures.^[48] In IIT and the green channels, China has two large pathways the United States does not have: an IRB-gatekept pathway that lets private actors go around regulators, and accelerated pathways that let officials work actively with sponsors to advance therapies using staged and interim evidence. In essence, China has optimized for fluidity and momentum.

C. The FDA paradigm as irrational path dependence

Reform in the United States is hampered by a deep-seated status quo bias that makes any real alternative seem inconceivable. Regulators, attorneys, and institutional healthcare providers often assume that any pro-innovation reform will unleash the “Wild, Wild West.”

Apologists for the current American system sometimes invoke the Massengill massacre. They also frequently invoke the thalidomide tragedy of the late 1950s—in which a West German anxiety medication caused over ten thousand children to be born with horrific and mostly fatal birth defects.^[49] In contrast to the Massengill massacre, which killed over a hundred American patients, thalidomide was never approved or sold in the United States. Strangely, thalidomide is often cited specifically to show that America’s pre-1962 system, before mandatory efficacy testing or formalized multi-phase trials, was insufficient.

The Massengill and thalidomide crises function as a kind of founding myth justifying universal, regulator-centered premarket multi-phase trials. Any reforms designed to expedite or create exceptions to this paradigm are often claimed, usually without elaboration, to put patients at risk of similar tragedies.

In fact—far from proving that the present system is necessary—basic animal testing could have exposed the lethal toxicity of Massengill’s solvent. Later experiments also demonstrated thalidomide’s teratogenic effects in particular animal models, although their ability to predict the human tragedy depended on the species and testing conditions.^[50] The thalidomide crisis in particular, far from showing that the FDA paradigm is necessary to prevent catastrophe, seems to show the opposite: thalidomide was never approved in the US even though the crisis predated both mandatory efficacy testing and the current “phase” system.^[51]

An unspoken assumption underlying the FDA paradigm seems to be that the US system has been carefully designed to strike a balance between safety and innovation. Yet comparing the divergent frameworks within the bio-tetrarchy forces us to ask whether substantial aspects of the American system truly serve any sensible purpose at all. As one US entrepreneur has put it, Australia’s safety record has exposed the “12–18 months of preclinical work” required by the FDA as a useless “Soviet legacy of the mid-20th century that is straitjacketing us and delaying innovation.”^[52] Some legal scholars have argued that the FDA paradigm is best understood as a product of historical accident, path dependence, and the natural tendency of regulators to amass power.^[53] This possibility points the way to alternative models that could better foster innovation while continuing to protect patient safety.

IVF: The last and first personalized biologic

Even in isolation, certain features of the American system suggest that it is better understood as a construct of irrational path dependence than of accumulated wisdom. The US government selectively declines to apply or enforce the FDA paradigm in multiple notable areas—including IVF, specific bulk drug substances, and food additives. These longstanding nonenforcement traditions cannot be explained by any consistent legal theory and must be the result of happenstance, political expedience, lobbying, or some combination of these factors. In any case, they serve as powerful demonstrations that not every aspect of the FDA paradigm is necessary to protect public health.

We have noted that, under the FD&C Act or PHS Act, *in vitro* fertilization and other forms of assisted reproductive technology fall within a literal reading of the definitions of “drug,” “biologic,” or both. The FDA has nonetheless historically classified IVF as a form of medical practice and thereby exempted it from regulator-gatekept premarket approval.

This does not mean IVF is “unregulated.” As a form of medical practice, IVF is subject to regulation by state licensing boards, medical malpractice liability, state regulatory rulemaking, and state statutory frameworks.^[54] These guardrails have evidently been enough to protect this sensitive area of biotech from the parade of nightmarish “Wild West” or “Frankenstein” outcomes that are invoked to justify the FDA paradigm. There has been no Massengill massacre or thalidomide crisis in American IVF. Assisted reproductive technology thereby lights the way to a future US paradigm for regulating individualized biologics of the kind already available in China.

Compounding pharmacies as favored child

Compounding pharmacies operate in a legal gray area made possible through a formalized tradition of enforcement discretion at the FDA. The bulk drug substances used by compounders—controversially including peptides^[55]—have two legal pathways to approval: completing the full FDA paradigm or being added to the FDA’s binding 503A Bulks List through notice-and-comment rulemaking. Yet this system is not enough for compounders to operate at their present scale.

Accordingly, the FDA has adopted an “Interim Policy on Compounding Using Bulk Drug Substances” in which it simply lists specific, unapproved peptides as quasi-approved.^[56] Although some media outlets describe this as a way for bulk drug substances to “become legal,” it is actually a nonenforcement policy rather than a species of lawful approval. While the word “Interim” is meant to suggest that these substances will eventually be placed on the 503A Bulks List through binding regulation, there is, in principle, no reason that a bulk drug substance cannot remain under the Interim Policy indefinitely.

The FDA’s nonenforcement policies around IVF and bulk drug substances arose for very different reasons. Myrisha Lewis, a leading legal scholar of assisted reproduction, has written that the FDA refrained from regulating IVF because “[t]he lack of consensus on IVF corresponded with a lack of federal regulation, which allowed IVF to flourish.”^[57] In contrast, the Interim Policy seems to have

arisen because compounding pharmacies operate as a well-organized and agile lobbying force at both the federal and state level. Perhaps ironically, the peculiar legal status of compounding pharmacies seems to have made them instinctively hostile to pro-innovation reforms that might upset the delicate balance of the Interim Policy framework by creating similar expanded access pathways for other sectors.

Food additives & GRAS: Innocent until proven guilty

If the policies governing IVF and bulk drug substances are unusual, the *ad hoc* regime governing American food additives can seem downright absurd. Theoretically, the FD&C Act is supposed to subject food additives—not just drugs—to a pathway of regulator-gatekept premarket approval. In reality, food additives are subject to much lighter regulatory burdens than drugs.

The “FDA paradigm” governing drugs and biologics is so wooden that it openly withholds drugs and biologics from the market even when nobody disputes that the article is safe.^[58] In contrast, the FDA sometimes allows food additives to remain on the market even when a substantial consensus exists that the additive is likely carcinogenic.

This disparate treatment might seem surprising. The name of the FD&C Act itself, after all, begins with the word “food.” Likewise, federal drug regulators are still called the “Food and Drug Administration”—not the “Drugs and Biologics Administration.” Yet the FDA’s own numbers show that it spends only 17% of its annual budget regulating food, 44% regulating drugs and biologics, and a further 12% regulating medical devices.^[59]

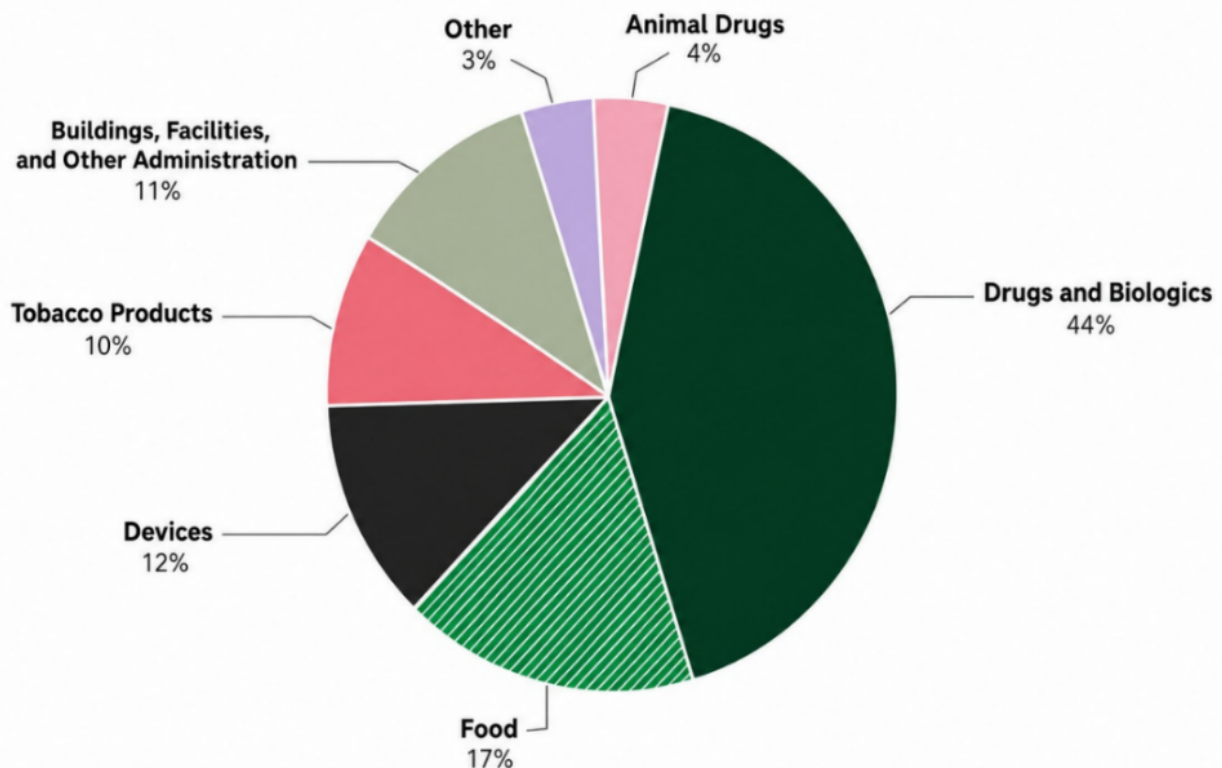
The legal explanation lies in § 201(s) of the FD&C Act, which defines a food additive to include only substances in food that are “not generally recognized, among experts qualified by scientific training... to be safe.” This broad carve-out is followed by some directly enumerated exceptions for pesticides, pesticide chemical residues in processed food, and color additives.

The exception for substances which are “generally recognized as safe”—and therefore factually but *not legally* “additives”—is today known by the acronym “GRAS.” This category forms the basis for much of the FDA’s loose regulation of food additives.

The FDA has had multiple systems for determining whether a substance is GRAS. Before 1997, the FDA maintained a list of additives it had determined were GRAS—roughly analogous to but legally distinct from the agency’s Interim Policy on bulk drug substances. Beginning in 1997, however, the FDA adopted a kind of sponsor-centered *de facto* approval system in which a sponsor—called the “notifier” in the GRAS context—submits expert testimony to the FDA explaining why it believes an additive qualifies as GRAS. Usually, the FDA simply acknowledges these submissions by responding with a “no questions” letter. This process was not codified in binding agency regulation until 2016.^[60]

In rare cases, the FDA issues a kind of formal disapproval by responding with a “no basis” letter. More commonly, the notifier itself withdraws the substance from consideration upon receiving questions from the FDA. Yet, unlike in biologic approval, GRAS is not premarket gatekeeping: even formally disapproved substances can still be lawfully sold as GRAS in the absence of full post-market adjudication.^[61]

"Food" and Drug Administration? FY2025 Budget by Program



Source: Distribution of FDA FY2025 Budget by Program and Source

The GRAS system is in some sense similar to Australian Clinical Trial Notification—and, to a lesser extent, to Chinese Investigator-Initiated Trials—in that all three paradigms are gatekept principally by private experts rather than regulators: the GRAS regime is often called “self-affirmation.”^[62] Yet GRAS is actually far *less rigorous* than either the Australian or Chinese biologics paradigm.^[63]

Both Australian CTN and Chinese IIT involve controlled trials conducted with the approval, and under the supervision of, scientific review boards. In contrast, a GRAS application is essentially a flexible package of real-world evidence submitted to satisfy an abstract standard of proof: “reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use.”^[64]

In practice, “reasonable certainty” is a low bar. For example, FDA regulations continue to affirmatively list the preservative butylated hydroxyanisole, or “BHA,” as a GRAS substance.^[65] Yet BHA has been categorized since at least 1991 as “[r]easonably anticipated to be a human carcinogen” by the National Institutes of Health—part of the same cabinet department as the FDA. BHA continues to be fed to millions of Americans in a variety of frozen food products by manufacturers like Hungry Jack^[66] and General Mills^[67] and is widely used in beef jerky products like Jack Link’s.^[68]

This disparity becomes more striking when we consider that, from the standpoint of objective harm prevention, it makes more sense to subject *food additives* to rigorous premarket approval than drugs or biologics. Suppose an American child is regularly fed Totino’s frozen pizza, a General Mills product containing BHA, and develops cancer. Even assuming the BHA in Totino’s directly caused the child’s cancer, an *ex post facto* remedy—such as tort liability—would be unlikely to help the child or his estate.

Even assuming the child’s parents thought to sue General Mills, the manufacturer’s attorneys could argue that a nebulous range of factors might have caused the child’s cancer. The lack of any acute, causal link between a carcinogenic food additive and one specific person’s cancer makes this precisely the kind of harm that, in principle, can only be prevented by mandatory *premarket* gatekeeping of the additive.

Now imagine the same child later receives immunotherapy for his cancer and is negligently killed by harmful effects of the therapy. This time, there would almost certainly be a demonstrable causal nexus between the immunotherapy and the child’s death—owing to the monitored and controlled environment of the therapy itself.

This illustration shows that drugs and biologics are precisely the kind of article that *can* soundly be regulated by *ex post facto* remedies like civil liability. From first principles, we might expect that therapeutic biologics would be regulated through medical licensing, tort liability, and other retrospective statutory and regulatory tools, while food additives like BHA would require prospective, product-specific approval through clinical trials.

The FDA paradigm, of course, does the opposite: many food additives, through pathways like GRAS, are effectively regulated only by retrospective mechanisms like civil liability that are qualitatively inadequate to ensure consumer safety. Yet biologics, which are needed to prevent sick patients from dying, must be subject to rigorous prospective approval.

Additives and drugs are also subject to perversely backwards burdens of proof. Food additives are presumed innocent until they are proven guilty, remaining on the market long after they are broadly recognized as likely human carcinogens. In contrast, the biologics needed to deliver patients from suffering and death are *presumed guilty* and withheld from the market until they are proven to be both safe and effective in a multi-phase trial process. This is especially tragic when we consider that, while biologics are often the only way to save the lives of sick patients, no particular food additive is ever necessary to feed any one person.

A system truly organized around harm prevention would apply its strictest gate where *ex post* remedies fail—on the carcinogen in the frozen pizza, whose injury is diffuse, latent, and nearly impossible to trace to any defendant—and its broadest gate to therapies administered under supervision in a monitored clinical setting. The FDA paradigm does the reverse, revealing that the system’s preference is not avoiding injury but its traceability. A death from an approved therapy is attributable—Massengill and thalidomide are remembered by name—while a death caused by a withheld therapy, or by a carcinogenic food additive, is not perceived as a policy failure. This revealed preference for avoiding traceable harm at all costs, even where doing so increases net harm, shows that the paradigm’s accretion has been shaped by short-term political incentives in ways that are irrationally path-dependent.

III. The Bio-Tetrarchy Compared

This section examines in more detail how the other great powers in the bio-tetrarchy—China, Australia, and Japan—regulate the general approval and reimbursement of drugs and biologics. The fact that these nations are able to offer both safety and efficacy with radically different systems exposes the arbitrary, path-dependent nature of the FDA paradigm. In certain respects, these nations also suggest models of reform for the United States.

This paper is not optimistic about the near-term prospects for a lawmaker-led, top-down overhaul of America’s entire three-phase regulatory framework—nor of the underlying FD&C Act and PHS Act. Many established interests, including pharmaceutical companies and regulators themselves, have been shaped by the current system, depend on it for their power, and have built their profit models around it. Not even the world’s first trillionaire could get Congress to enact more than ~5% of the DOGE cuts.

Still, while not every desirable characteristic of our peer nations can be replicated in the United States in the short term, considering the examples of China, Australia, and Japan does point the way to specific, realistic reforms that could synthesize most core lessons of the bio-tetrarchy without radical Congressional action.

A. China: Optimizing for fluidity

China is still considered to be a slower regulator than the US, with approval timelines generally lagging behind the US, Japan, and even the EU. Over the five-year period from 2019 through 2023, however, China approved the highest number of new drugs, clearing 256—more than the United States, Europe, or Japan.^[69] China is also rectifying its approval-time lag: after 2021, the lag between Chinese and American approvals of the same drug fell by nearly half, while the gap behind Europe fell by 83%.^[70]

Goldman Sachs reports that roughly a quarter of the innovative drug candidates now in active development worldwide originate in China—and that 46% of all new molecules entering human trials in the first half of 2025 came from Chinese companies, up from about 17% a decade earlier.^[71] China enjoys particularly dominant leads in several specific areas. For example, over the preceding two and a half years, Chinese firms accounted for something like 70% of global antibody-drug-conjugate development and 60% of bispecific antibodies.^[72]

China has also established undisputed global leadership in CAR-T therapy, or chimeric antigen receptor T-cell therapy—a form of cancer immunotherapy that re-engineers a patient’s own immune cells to attack the patient’s cancer. By 2022, China had registered 188 CAR-T trials in leukemia against 99 in the United States, 234 trials in lymphoma against 159 in the US, and 64 in plasma-cell myeloma against 55 in the US.^[73]

One oncologist attributes this disparity partly to the Chinese regulatory system, in which individualized therapies are often categorized as medical practice—and hospital review boards approve IITs without centralized regulator gatekeeping. Chinese trials can therefore use CAR-T cells produced locally at a medical center or in collaboration with a small biotechnology company, in contrast to the US—where winning FDA approval “requires large, complex, expensive clinical trials.”^[74]

China is also cheaper and faster at the basic work of generating clinical evidence. In Phase 3 non-small-cell lung cancer trials, the direct cost per patient is roughly \$69,000 in the United States against just \$25,000 in China.^[75] To be sure, these advantages are not all due to legal structure: China enjoys the benefits of lower wages and a vast pool of patients clustered in urban regions near large hospitals, which lets a single institution fill a trial many times faster than its American counterpart.

China is also a world leader in clinical firsts. In several cases, China has treated patients with first-in-human frontier therapeutics while the analogous American product was either refused, abandoned, or delayed by years. The explanation is frequently a structural feature of China’s regulatory paradigm that the United States lacks.

China's first-in-human therapeutics

In 2016, a team led by oncologist Lu You became the first in the world to inject a human being with cells edited by CRISPR-Cas9 to treat metastatic non-small-cell lung cancer. The hospital's own review board approved the study on July 6, 2016, under China's IIT framework—and the first patient was dosed that October.^[76] Of twenty-two patients enrolled, twelve ultimately received edited cells.

The American counterpart study, at the University of Pennsylvania, did not dose its first patient until 2019—and reported only three—after clearing an NIH advisory panel, the FDA, and the university's own review board in succession.^[77] This delay was not a coincidence. The University of Pennsylvania is the institution where, in 1999, eighteen-year-old volunteer Jesse Gelsinger died of an immune reaction to an adenoviral vector, unleashing liability in the form of an undisclosed settlement, prompting the FDA to suspend the institution's gene-therapy trials, and chilling the American gene therapy field for a decade.^[78] Both CRISPR trials passed serious ethical review: the key difference was that China treated the therapy as a medical technology, while the American system subjected CRISPR to the full FDA paradigm.

China has also been a first-in-human leader in oncolytic viruses, engineered to replicate inside and burst tumor cells. While limited by tumor accessibility problems, these viruses are highly effective when a provider can reach the cancer with a needle. In November 2005, Chinese regulators approved a therapy called H101, or “Oncorine,” for nasopharyngeal carcinoma in combination with chemotherapy: the world's first approved recombinant oncolytic virus. Its Phase 3 data showed a response rate near 79% for the virus-plus-chemotherapy arm against roughly 40% for chemotherapy alone.^[79] The nearly identical American construct, ONYX-015, was never approved by the FDA—nor has anything quite like H101 ever been approved for the same use in the United States.^[80]

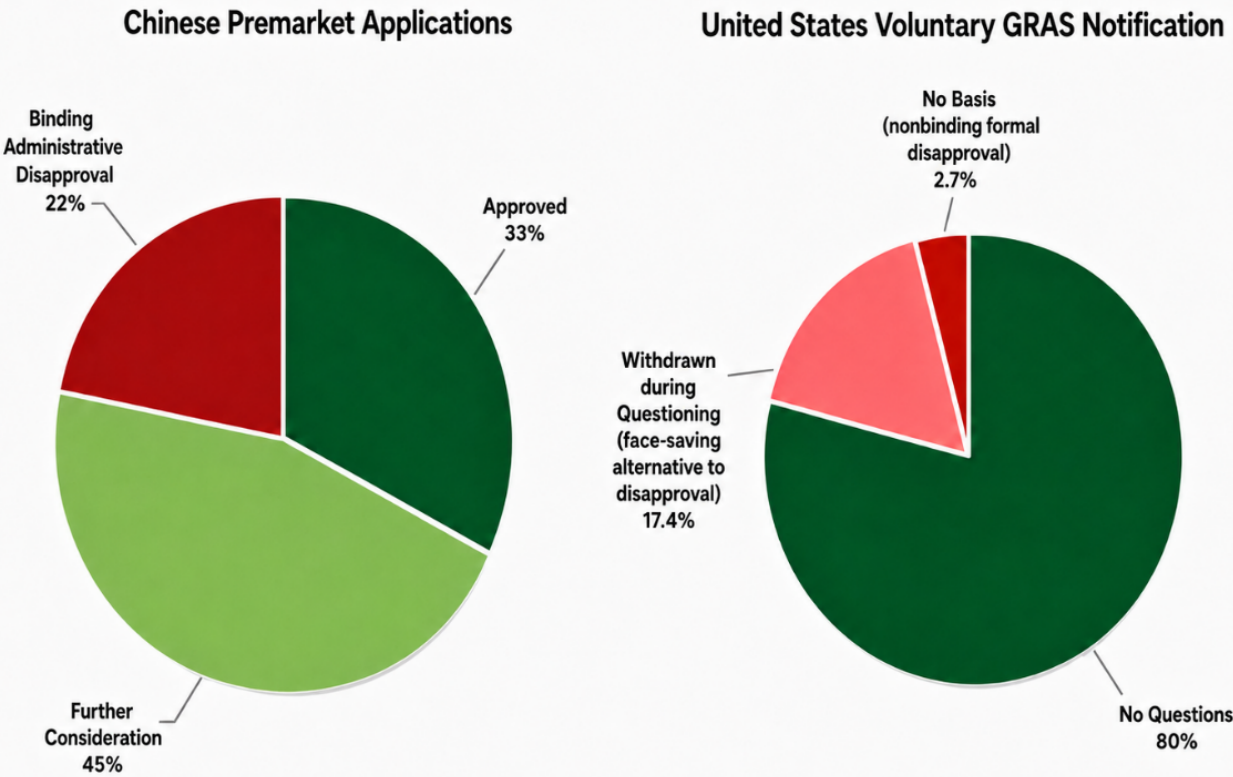
While China's pro-biotech turn is in some respects a recent phenomenon, its tendency to achieve first-in-human translation is not. In 2003, China issued a drug license to Shenzhen SiBiono GeneTech for Gendicine, a recombinant adenovirus delivering wild-type *p53* to treat head and neck squamous cell carcinoma; GMP clearance and commercial launch followed in 2004. It was the first gene therapy product approved anywhere in the world for clinical use.^[81]

Over the twelve years that followed, Gendicine was used in more than thirty thousand patients across more than thirty published clinical studies, compiling what its developers call an exemplary safety record—no serious adverse events beyond a transient, self-limiting fever in half to sixty percent of recipients.^[82] The United States never approved Gendicine, and a closely analogous American product, Introgen Therapeutics' Advexin, drew an FDA “Refuse to File” letter in 2008, after which the company collapsed into bankruptcy.^[83]

The result was Western medical tourism to China. Terminally ill patients from Europe and America traveled there to obtain a therapy they could not buy at home. Reliable counts do not exist—trade reporting puts the foreign cohort at roughly twenty in the drug’s early years and at “hundreds” by the end of the decade—but the general trend was well-known.^[84]

Americans unfamiliar with contemporary China might assume that China only excels in first-in-human therapeutics because—as an authoritarian government—it is willing and able to sacrifice the safety of its population in a relentless drive for technological progress. A range of metrics, however, suggests that this is not true. Whatever the Chinese government’s other faults, Chinese health regulators appear to be serious and competent. China issues formal disapprovals to food additives, for example, at rates at least competitive with the United States—and its substantive regulation of food additives is more stringent than America’s.

Regulatory Outcomes for Food Additives



Source: CIRS, Analysis on the Application and Approval of New Food Additives in 2024, CIRS Group (Jan. 24, 2025)

The sobering reality is that China is gaining on the United States not because it is cheating, but because it has energetically constructed a near-optimal legal framework for approving safe and effective biologics. In contrast, the United States’ FDA paradigm is patently deficient but often immune from serious mainstream criticism.

Thanks to path dependence and status-quo bias, any more-than-marginal proposed reform to the FDA paradigm is often assumed to be crankish or dangerous. Comparing the diverse legal frameworks of the bio-tetrarchy—including China’s—is critical to persuading American policymakers to rethink this baseline assumption. The Chinese example should give Americans the political permission to seriously consider significant reforms in order to retain America’s competitive edge and reestablish clear leadership in biotechnology.

China’s pro-biotech turn

China’s achievements reflect a deliberate, expanding pattern in which China’s government has crafted ambitious packages of pro-innovation reforms.^[85] One of the most consequential of China’s reforms was the creation of its recent “green channel” pathways. These were first codified in China’s 2020 Provisions for Drug Registration and rearticulated in the 2026 Implementing Regulations of the Drug Administration Law.^[86]

The “green channel” concept includes four distinct procedures: breakthrough therapy, conditional approval, priority review, and special approval. The breakthrough therapy procedure offers rolling submission and intensified regulator guidance for drugs treating serious or life-threatening conditions. The conditional approval procedure permits marketing on the strength of a surrogate endpoint rather than completed outcome data—subject to post-market confirmation. The priority review procedure expedites innovative drugs and treatments for rare and pediatric disease. And the special approval procedure handles public-health emergencies, as it did during COVID-19. Together, these four procedures are meant to be the “equivalent to opening a ‘green channel’ for new drug R&D.”^[87]

Green channel	Function
Breakthrough Therapy	Rolling submission for serious or life-threatening conditions.
Conditional Approval	Marketing on a surrogate endpoint, pending confirmatory evidence.
Priority Review	The destination pathway, with hard statutory clocks; Breakthrough and Conditional both feed into it. Covers innovative and rare-disease drugs.
Special / Emergency Approval	Emergency pathway (e.g., COVID-19); the principal driver of China’s 2021 approval surge.

These 2020 reforms help explain why 2021 was an inflection point in China’s approval lag time. The upshot is that the green channel gives regulators tools to accelerate promising therapies through staged evidence review, intensified guidance, and conditional approval. Sponsors still apply for the procedures, and conditional approvals require post-market confirmation; the framework does not amount to unrestricted *sua sponte* approval. In other words, China wants its regulators to propel therapies through the approval process while America’s regulatory paradigm is oriented towards holding therapies back.

China’s biotech revolution does not start and stop with the green channel pathways. In December of 2024, China’s State Council issued a blueprint of twenty-four reform measures to accelerate innovation, including a pilot program compressing IND applications from sixty to thirty days.^[88] In April of 2025, the Beijing municipal government issued its own “Several Measures to Support the High-Quality Development of Innovative Medicines,” taking the central State Council up on its offer and cutting the processing of investigational drug applications in half.^[89] Anyone familiar with policy advocacy in the United States will know that it is impossible to imagine a state government crafting and implementing any pro-innovation public health reform this quickly.

During the period in which China has aggressively pursued pro-innovation reforms, the United States has also pursued some reforms intended to expand access to experimental therapies. Yet America’s halting reforms have amounted to nibbling at the margins.

America’s 2018 federal Right to Try law is a textbook example. That law, while falsely purporting to create an expanded access pathway for sick patients, explicitly incorporated 21 C.F.R. § 312.8(d)(1). This provision directly prohibits a provider from profiting from an experimental therapy—making ordinary commercialization impossible and rendering the law meaningless in the eyes of most providers. FDA reporting shows that the federal law was used 21 times from its enactment through 2024.^[90]

A newer entrant, the FDA’s proposed “plausible mechanism” framework for individualized therapies—based on the successful treatment of KJ Muldoon—is more promising but still halting. That framework proposed that candidates for individualized therapies could confirm that a target was successfully drugged or edited with “mouse models” or equivalent nonanimal models in order to obtain *ex ante* regulator-gatekept approval. This framework does not provide anything approaching a viable pathway for commercializing individual therapies at scale.^[91]

In contrast, individualized therapies are an area where China is poised to excel. Under what some call a dual-track system, a Chinese cell or gene therapy may be developed under one of two paths. If the therapy is a biologic, it is regulated by the National Medical Products Administration, requiring a formal IND application and a biologics license. If the therapy is a biomedical technology—best

understood as a kind of medical practice—it can begin an investigator-initiated trial on the strength of a hospital review board’s approval without central regulator gatekeeping. From there, a personalized biomedical technology now enjoys a regulatory fast-track to commercialization.

By one accounting, such non-IND investigator-initiated trials already outnumbered the formal regulatory track by a factor of more than fourteen from 2000 to 2021.^[92] Chinese innovators have learned to exploit the track for exactly this purpose; as one trade analysis notes, “many cell and gene therapies have been leveraging the IIT for fast proofs of concept.”^[93]

Order 818 and Mei

On May 1, 2026, Order 818 went into effect. This new framework, promulgated by China’s State Council, is aimed at standardizing the IIT system for a range of frontier technologies from gene therapy to brain computer interfaces. While the rollout of Order 818 has disrupted some ongoing IITs,^[94] the order is broadly aimed at promoting IITs and expanding their commercialization.

Unlike the top-down rollout of the green channel pathways, China’s IIT system is a more organic phenomenon that has evolved with relatively little centralized planning. By reorganizing and formalizing IITs through Order 818, China’s State Council has reaffirmed the pathway as a strategic asset for biotech innovation.

The order adds some additional guardrails to the IIT pathway, restricting the range of hospitals eligible to authorize the trials and—like under the Australian model—requiring the hospital to notify regulators that they have approved a trial.^[95] Yet the framework preserves the ability of private institutional review boards to authorize human trials and, more importantly, codifies a paid pathway to commercialization for personalized biologics.

The Order 818 framework uses the term “biomedical technology” to differentiate personalized therapies from ordinary drugs and biologics. Under the Order and its implementing Work Specifications, these technologies enjoy a rapid pipeline from a single IIT to full commercial approval. If a technology’s “degree of personalization is high,” or if it treats a rare disease, a completed IIT’s results may be submitted for review by a publicly-funded “professional institution”—a process that China’s National Health Commission can accelerate further through emergency or priority review.^[96] After receiving the professional institution’s opinion, the National Health Commission must then make a binding decision on the applications within 15 working days.^[97]

Notably, the National Health Commission—the one centralized gatekeeper in the Order 818 pathway—is not China’s version of the FDA. China’s FDA analogue is the National Medical Products Administration, which gives premarket approval to drugs and biologics. In contrast, the NHC is focused on regulating medical practice. By placing personalized biomedical technology under the

purview of the NHC rather than the NMPA, China is reaffirming a meaningful boundary between its drug paradigm and the sphere of medical practice—exactly the distinction that the US has dissolved—and formalizing personalized biomedical technology as something akin to medical practice.

In the months since the rollout of Order 818, IITs have recently attracted unprecedented attention in the West for the wrong reasons. In July 2026, a joint investigation by *Science* and Retraction Watch reported on the death of a 6-year-old girl—described by the investigation as the first person to receive a gene-editing therapy directed at the brain—in an IIT.^[98]

In late March 2025, about a month after the successful treatment of KJ Muldoon, 6-year-old “Mei” was the subject of a single-patient gene therapy IIT for Snijders Blok-Campeau syndrome—a rare genetic illness. As Mei grew, she may have developed intellectual disabilities, seizures, heart problems, and an enlarged head containing fluid-filled voids.^[99]

After learning of her condition when Mei was 4, her parents began to privately fund an IIT led by neuroscientist Zilong Qiu.^[100] Like Jesse Gelsinger, Mei reportedly died following a severe immune reaction linked to the therapy’s viral delivery mechanism.

Qiu conducted preclinical efficacy and safety testing in mice and monkeys before receiving approval from an IRB at the prestigious Xinhua Hospital. While some secondhand reports have suggested that Qiu was paid handsomely for the research, *Science* and Retraction Watch reported that Qiu made no profit from the trial and “never asked for anything himself.”^[101]

Although Qiu’s base editing therapy worked in mice, safety testing on monkeys showed a potentially dangerous immune reaction to the therapy’s viral delivery mechanism.^[102] In July 2026, *Science* reported that the hospital’s IRB had not examined the results of this toxicology study.

Science’s reporting on Mei’s death emphasized the IIT structure—and its differences from the FDA paradigm—as a factor in Mei’s death. The report’s author even states that the therapy “might have gotten more scrutiny if the trial had been reviewed... by the National Medical Products Administration—China’s version of FDA—rather than an investigator-initiated trial.”^[103]

The report did not note the integral role that IITs have played in China’s progress in biotech, that IITs are generally rigorous and safe, or that Lu You’s world-first CRISPR trial was also an IIT approved without central regulator gatekeeping.^[104] Nor did the report ask whether treating patients like Mei would even be possible at scale under an FDA-like regulator-gatekept paradigm.

In the months before *Science*’s report, in fact, innovators had welcomed the expanded commercialization of IITs as a necessary step to scaling individualized therapeutics. Genetic Engineering & Biotechnology News, summarizing a discussion with a Singaporean investor, reported that “Because advanced therapeutics are intricate and often personalized, it’s quite difficult for them to use the standard NMPA pathway.”^[105]

Coverage of Mei's death highlights the mental architecture surrounding the FDA paradigm. In their reporting, *Science* and Retraction Watch quoted a bioethicist who issued familiar warnings that we must not become "blinded by hope" in frontier therapies. In an editorial, *Science* said Mei's death raised questions about China's attempt to "speed research into human therapies."^[106]

These commentators discussed Mei's death as if innovation were a one-dimensional tradeoff between safety and speed. None of these voices acknowledged the unknown number of patients who suffer because regulation slows or obstructs emerging therapies. Patients just like Mei who die precisely because innovation is slowed—a group that some have called the "invisible graveyard"—were effectively assumed not to exist.^[107]

In the same way, some US-based journalists reacting to Mei's death took the FDA paradigm as a norm and presented IITs as a kind of loophole.^[108] In reality, China, Australia, and Japan all have IRB-gatekept trials: it's America's one-size-fits-all system that's exceptional.

B. Australia: The Silk Road of Phase 1 trials

Australia is, in some respects, the junior partner in the bio-tetrarchy. It approves new drugs more slowly than the United States, hosts a fraction of America's absolute trial volume, and has neither China's scale nor Japan's commercialization machinery. Yet companies increasingly choose Australia for their first human trials. Australia ranks 1st in the world for the initiation of commercially sponsored clinical trials per capita, 3rd globally for total number of Phase 1 clinical trials initiated, and has more per capita clinical trial activity than the United States.^[109]

Under Australia's Clinical Trial Notification system, the sponsor does not petition the Therapeutic Goods Administration—Australia's version of the FDA—for permission to begin. It instead secures approval from a "Human Research Ethics Committee," an institutional review board, and then simply files an electronic notice with the TGA. Upon submission of the form and payment of a fee, the trial is, in the language of the regulations, "deemed to have been notified."^[110] There is effectively no centralized agency gatekeeping at the IND phase of developing a therapeutic.

The TGA does not re-review the protocol, the investigator's brochure, or the underlying data; that scientific and ethical gatekeeping belongs to the IRB.^[111] The agency's role is simply to acknowledge the notification, which practitioners describe as ordinarily arriving within two weeks and often within days; TGA guidance expressly says recruitment need not await the acknowledgment.^[112] With ethics review and institutional governance running in parallel, a sponsor can move from final protocol to first patient in roughly six to twelve weeks.^[113]

For a narrow class of products—typically cell and gene therapies never before administered to humans and lacking prior review abroad—Australia channels the sponsor into a Clinical Trial Approval pathway in which the TGA does examine product-level data before the trial proceeds. Practitioners describe this as “a mini IND.”^[114] This is the kind of calibration that the US paradigm, which forces every physical article into a single framework, fails to make.

Australia also helps sponsors pay for trials through its Research and Development Tax Incentive. For companies with aggregated annual turnover below twenty million Australian dollars, the program furnishes a refundable tax offset at 18.5 percentage points above the company tax rate—so a firm taxed at twenty-five percent recovers over 43% of eligible research spending,^[115] with a proposed increase to 48%.^[116] The fact that this tax offset is “refundable” is important: a pre-revenue biotech with no tax liability—which is to say nearly every early-stage biotech—receives the credit as a cash payment from the government.^[117]

This framework has given rise to entire sub-industries. Because there is a 12-18 month lag between research spending and receiving the refundable tax credit, specialized Australian lenders offer “RDTI loans” against the expected rebate; one cited arrangement advances up to 80% at a 16% annual interest rate.^[118]

Australia’s early-trial system is domestically controversial and is the subject of recurring political attack by fiscal hawks—but industry advocacy group AusBiotech has lobbied vigorously and successfully to defend the program. While the United States has life sciences lobbying associations, there is no similar national, organized political force in the US invested in expanded access frameworks. Instead, those major institutions that are not invested in *defending* the FDA paradigm usually treat it as an immutable law of nature.

Australia’s two critical instruments—an IRB-centered, IIT-like regime and a refundable cash rebate—combine into an “Aussie shell” strategy that American sponsors have learned to exploit with some sophistication.

A United States biotech company will often incorporate an Australian subsidiary, run its Phase 1 trial there cheaply and quickly, collect the rebate as cash, and then repatriate the resulting data to support an IND application back home for larger trials. Alternatively, companies may parlay the results from their Australian Phase 1 trial directly into the conditional-approval on-ramp in Japan, allowing them to rapidly commercialize the therapeutic.

The data travels because Australian trials are conducted to international standards the FDA accepts; the sponsor need not repeat the early work on American soil.^[119] The cost differential that drives all of this is significant: Australia runs early-phase trials at roughly twenty-eight percent below American

cost before incentives—and roughly sixty percent below after them.^[120] Individual sponsors report still steeper savings—although these figures often fold in currency effects and should be read cautiously.^[121]

Aussie-Japan Pipeline	
Phase 1 Launch	Australia: CTN allows sponsors to begin after HREC approval and TGA notification.
Trial Financing	Australia: Refundable R&D tax incentives help finance early trials and extend runway.
Data Export	Australia → Japan / U.S.: Australian trial data can support later development abroad.
Early Commercialization	Japan: Conditional approval and related pathways can enable earlier market entry.
Reimbursement / Access	Japan: National Health Insurance can help make approved therapies broadly accessible.
US Market Later	United States: The US remains the large prize, but often after foreign early evidence and/or foreign commercialization.

The result is that a mid-sized country has made itself the world’s preferred laboratory for the most speculative stage of drug development. Australia attracts Western sponsors seeking China’s regulatory flexibility and Chinese sponsors seeking access to the American market.

America does not need to copy Australia wholesale to learn from it. Australia is, if nothing else, a demonstration that we need not set up a false choice between the FDA paradigm and the “Wild West” that FDA-paradigm apologists reflexively invoke.

C. Japan: Insurance as substrate for innovation

Japan is well-known for its conditional approval pathway.^[122] The Pharmaceuticals and Medical Devices Act created one in 2014 for “regenerative medical products”—a distinct legal category covering more-than-minimally-manipulated cells and gene therapies,^[123] letting a sponsor market a product on presumed efficacy while it gathers confirmatory data. This 2014 regulatory package also included several reforms designed to expedite regulatory review,^[124] including an IIT-like pathway.

In 2017, Japan expanded the conditional-approval framework to other categories of drugs.^[125] American firms use this pathway: Pfizer’s cancer therapy lorlatinib, for instance, reached Japanese patients through the conditional route.^[126] The decisive Japanese advantage comes after approval, when a therapy becomes eligible for insurance reimbursement.^[127]

Japan has had universal insurance coverage since 1961, administered through a pool of insurers that nonetheless operate under one uniform payment system.^[128] Prices are not negotiated insurer-by-insurer. They are set centrally, at a single national price—and once a product is listed on the national schedule every insurer in the country must reimburse it at that price.^[129]

Jurisdiction	After regulatory approval	Character of the gate
Japan	Near-automatic national listing in roughly 60–90 days, no cost-effectiveness gate at entry.	The softest gate; approval normally leads promptly to national reimbursement.
China	Annual, competitive, steep-discount NRDL negotiation; new commercial list for high-cost gene therapy.	The hardest price gate, but fast and population-wide once won.
United States	An uncoordinated, indefinite, payer-by-payer process with no national decision at all.	No single gate—an open-ended gauntlet.

Listing follows approval as a matter of administrative course—for a drug-classified product, normally within sixty to ninety days, although some listings take longer.^[130] Some commentators have observed that Japan’s insurance framework “allows patients to receive immediate access to innovative treatments.”^[131] This Japanese framework, whatever else one thinks about centrally managed insurance prices, has acted as a kind of loam for innovation in biotechnology.

This should sober American reformers, because this is a part of the Japanese system the United States is nowhere close to having. FDA approval—accelerated or ordinary—guarantees nothing about whether a patient can obtain the therapy.^[132] At least one insurer has announced plans to sit on accelerated-approval products for eighteen months before paying for them.^[133] In the United States, the regulators’ gate is not the payors’ gate. In Japan, national reimbursement listing normally follows the regulatory decision.

It is this predictable route to national reimbursement, more than any other, that draws Western companies to commercialize in Japan. While Pfizer reached Japanese patients with lorlatinib through the conditional pathway,^[134] Eli Lilly and Moderna reach them through ordinary approval. Their approved drugs ordinarily reach the national insurance schedule within about three months and are reimbursed under a uniform national framework.

This disparity between Japan and the US is, unfortunately, not fixable by any marginal or moderate reform. Aligning US insurance with Japan's would require a top-down and unwavering effort to push sweeping reforms through Congress. Since this is not achievable in the near term, it is all the more critical that the interim reforms we do advocate be both realistic and ambitious. America must engage in creative policy innovation in order to compete in the bio-tetrarchy.

IV. Regulating Other Frontier Technology

We've seen how America's regulatory pathologies include the reflex to classify every novel article as a drug or biologic, a commitment to a one-size-fits-all approval pathway, and a reliance on regulatory grace rather than on fixed policy. Similar difficulties confront a range of frontier technologies.

In this section, we examine some much-discussed technologies: peptides, chimeras, synthetic embryo models, bodyoids, and mitochondrial replacement therapy. In most cases, we will identify how the American regulatory paradigm might impede the technology and—usually drawing on the policies of peer nations—propose reforms that could clear the obstruction.

A. Peptides

Peptides are the most instructive existing model for how a *sua sponte* real-world-evidence pathway could be built in the US without a top-down overhaul of American law. They are also, incidentally, one of the few therapeutic articles that are legally *not* biologics. This is due to a quirk of statutory happenstance.

Under the PHS Act, a “biological product” includes a “protein” but not a “peptide.” FDA’s binding regulatory definition of “protein,” rather than colloquial usage, is the boundary: an alpha amino acid polymer with a specific, defined sequence greater than 40 amino acids in size. Shorter amino acid polymers generally fall outside that protein definition and are instead regulated as drugs under the FD&C Act. A polymer of 40 or fewer amino acids is therefore a peptide and is regulated as a drug.^[135]

As we observed earlier, peptides have come to be regulated under a two-layer structure created more by FDA policy than by statutory or regulatory law. Legally, a compounding pharmacy may use a bulk drug substance that lacks a monograph and is not part of an approved drug only if the substance appears on a list the FDA develops through notice-and-comment rulemaking—the list codified at 21 C.F.R. § 216.23.^[136]

Yet the FDA has also chosen to administer an “interim policy” sorting substances into Categories 1, 2, and 3—describing where it will and will not exercise enforcement discretion.^[137] Even a quasi-legal Category 1 substance is—strictly speaking—not lawfully compoundable: it is merely tolerated. The agency has promised not to act but is free to change its mind.

This was underscored in September 2023 when the FDA swept a roster of popular peptides—BPC-157, TB-500, CJC-1295, ipamorelin, and others—into Category 2 of its Interim Policy, declaring them significant safety risks. It did so not by rulemaking but by updating a webpage. Compounding pharmacies had to stop overnight; demand migrated to a gray market of “research-use-only” powders, much of it imported from Chinese manufacturers.^[138]

The example of peptides shows that written, *sua sponte* nonenforcement guidance can allow the FDA to effectively set policy pending final rules—the closest existing American analogue to the Chinese green channel. Creating a parallel policy framework for drugs and biologics is one means by which the United States could stand up a partial green channel for promising drugs and biologics on flexible forms of evidence—without waiting on Congress.

B. Chimeric tissues

A “chimera,” in the relevant sense, is made by introducing human stem cells into an animal embryo—a technique that could, in principle, grow human organs for transplant inside animals. Chimeras are distinct from contemporary xenotransplantation, in which an animal’s own organs are genetically edited to evade human rejection.

When it comes to chimeras, Japan is a leading force in the bio-tetrarchy. In 2019, its science ministry lifted prohibitions on developing human-animal chimeric embryos beyond fourteen days and permitted their gestation in surrogate animals while prohibiting their gestation in humans—a step the International Society for Stem Cell Research greeted as opening the door to growing human organs for transplantation.^[139] Japan, in other words, built an affirmative pathway through prospective guidance.

The United States neither explicitly permits nor prohibits chimeric tissues. Instead, the field is governed mostly by NIH funding policy, which withholds federal money from introducing human pluripotent cells into non-human primate embryos or from breeding animals in which human cells might reach the germline—layered atop the Dickey-Wicker Amendment’s bar on federal funding for research that creates or destroys human embryos.^[140]

Other nations have contrasting policies in both directions. Several jurisdictions ban chimeras outright by criminal statute—Canada, Australia, Germany, and the United Kingdom prohibit the placement of a human-admixed embryo into an animal.^[141]

The United States could adopt a federal guidance framework analogous to Japan’s, prospectively authorizing chimeric tissues created under appropriate ethical oversight for the purpose of developing methods of organ-growth. This could be effectively done through agency guidance from HHS or FDA.

C. Embryo models

In synthetic embryos, also called embryo models, human pluripotent stem cells are coaxed to self-organize into structures resembling early embryos—blastoids, gastruloids, embryoids—without fertilization, using no egg, sperm, or womb. They offer routes to studying early development and disease without “real” embryos and, like chimeric tissues, are one avenue that could point us in the direction of ethical replacement human tissues.

While the United States has no statutory or regulatory prohibition and no adverse court rulings on point, the Dickey-Wicker Amendment limits federal funding by defining an embryo to include any “organism” derived “by fertilization, parthenogenesis, cloning, or any other means” from human gametes or diploid cells.^[142] NIH examines the experimental details of embryo-model research on a case-by-case basis to determine whether it can support a proposal under the statutory funding restriction.^[143]

The critical question is therefore whether an embryoid is an “organism.” Some commentators draw the line by saying that an embryoid is not an “organism” so long as it lacks “organismic wholeness,” but this is ambiguous. A sharper distinction is *autonomy of self-organization*—whether the entity *self-initiates* spatial and temporal organization or has that organization *induced* within it by external chemical signals.^[144]

Australia uses a model-specific boundary. Its Embryo Research Licensing Committee asks whether an entity arose from a process that “initiates organised development” and has made model-specific determinations. Australia has accordingly determined that, for example, iBlastoids meet the definition of “human embryo” and require a license, while the Moris 3D gastruloid model does not, as it lacks the extraembryonic cell lineages needed to form an intact conceptus with the full complement of parts of a normally developing embryo.^[145] HHS or NIH guidance might clarify which embryo models lack the developmental completeness necessary to qualify as human organisms.

Our own conversations with industry participants, however, suggest that Australia’s distinction does not go far enough to provide a secure and scalable pathway for embryoid research. One solution might be to draw the boundary at the capacity to develop into a whole live-born organism—an important ethical boundary.^[146] We would favor language that presents an objective biological boundary to legislators and courts, with scientific evidence serving as the means of determining whether a structure meets it.

D. Bodyoids

The term “bodyoids” emerged from a March 2025 opinion essay in *MIT Technology Review* in which authors Carsten Charlesworth, Henry Greely, and Hiromitsu Nakauchi sketched the possibility of “spare” human bodies engineered never to develop neural architecture and therefore not to possess consciousness.^[147] The authors presented this idea as a method to conduct more accurate and ethical research, without the need for cadavers or animal studies, as well as to solve the organ supply crisis.

The authors presented this concept as a hypothetical extension of synthetic embryo technology—but, in theory, any human body developed without neural architecture could constitute a bodyoid. The authors noted that we do not know whether human bodies can actually survive and grow without neural architecture and—even if they can—whether these bodies could “serve as accurate models for living people without those brain functions.”

This disclaimer brings to mind the 2005 science fiction film *The Island*, in which a villain portrayed by Sean Bean claims to grow individual bodyoids for wealthy human customers. In fact, the antagonist is secretly harvesting organs from conscious clones—something he explains has turned out to be the only viable way to produce suitable human organs.

If unconscious bodyoids turn out to be scientifically practicable, where would they fit into the law? The MIT Tech Review authors essentially assert that bodyoids would be legally analogous to a human cadaver or chimeric tissue—but reality is unlikely to be that simple. Facilitating innovation in this area will require some clear and prospective legal framework to give assurance to investors and innovators.

Every state has adopted some version of the Uniform Anatomical Gift Act, which authorizes the donation of all or part of a human body, effective after the donor’s death, for the purpose of transplantation, therapy, research, or education.^[148] The UAGA is the primary statute governing American transplantation. One could imagine a legislature simply extending the gift framework—defining a “bodyoid” as a stem-cell-derived human biological construct that lacks organized neural structures and providing that such a construct may be used for transplantation, therapy, research, or education in the same manner as an anatomical gift.^[149]

The law governing the human body presumes a sharp line between persons and parts. An innovator could theoretically trip over this line by accident and be flung from the world of regulation and into the realm of criminal liability. History shows that the mere possibility of this occurring, however farfetched, could be enough to block life-saving innovation. As a theoretical but probable near-future technology, bodyoids present an opportunity for US states to innovate and craft forward-thinking policy before other nations. Policymakers should follow the general example of Japan and Australia concerning chimeric tissues and embryo models and craft bespoke guardrails to facilitate ethical innovation.

E. Mitochondrial replacement therapy

Mitochondrial replacement therapy (“MRT”) is a clean illustration of the gap between American and peer regulation. MRT is not speculative: it works, has produced healthy children, and it is effectively unavailable in the United States by act of Congress.

MRT replaces a mother’s defective mitochondria to prevent the transmission of devastating mitochondrial diseases such as Leigh syndrome. The United Kingdom, after a deliberate public process, authorized the technique through its Human Fertilisation and Embryology Authority, and British children have since been born free of the mitochondrial disease they would otherwise have inherited.^[150]

In the United States, the same appropriations rider that blocks germline editing also obstructs mitochondrial replacement: the FDA is prohibited from even accepting an application involving a heritable genetic modification of an embryo. Because the FDA takes the position that any heritable genetic modification to an embryo is a “biologic,” it is effectively illegal to market such a modification without FDA approval and hence, thanks to a Congressional appropriations rider, categorically illegal to do so in the United States.

In effect, a proven therapy that prevents fatal childhood disease in Britain is unavailable to American families thanks to a three-legged stool of interlocking legal problems: the Congressional budget rider, the FDA’s interpretation, and the federal statutory requirement that “biologics” be subject to premarket FDA approval.^[151]

Fortunately, removing any one leg of this stool would cause it to fall over. Even without any pro-innovation action by Congress, the FDA itself could authorize MRT simply by reversing its position that all heritable embryo modifications are biologics. If FDA guidance clarified that embryonic gene correction is lawful within certain parameters, at least including MRT, then MRT would become lawful in the United States.

V. Four Realistic Reforms

We’ve observed that dramatic, top-down Congressional reform in America—such as overhauling the FD&C Act or PHS Act, rewriting the three-phase trial regime, or transforming American health insurance into a Japanese system—would require extraordinary willpower and political force. In the meantime, however, it’s possible to synthesize many of the core lessons of the bio-tetrarchy through four relatively realistic reforms.

For most of the following reforms to work, a US president would only need to ensure that HHS and the FDA are staffed from top to bottom with determined pro-innovation personnel. Agency policy alone could replicate key aspects of Australian CTN and Chinese IITs as well as create *de facto* green channel pathways. With further, modest Congressional action, Congress could largely replicate the green channel structure and potentially end America’s drug-and-biologic monomania for good.

1. A Cole Memorandum for Biotech

First, the President, the Department of Health and Human Services, or the FDA could issue an executive order or policy letter modeled on the Cole Memorandum.

In 2013, Deputy Attorney General James M. Cole issued a memorandum directing federal prosecutors to focus on eight enforcement priorities and generally rely on effective state regulatory systems outside those priorities, while retaining federal enforcement authority. The Cole Memorandum, now formally rescinded, nonetheless effectively created today’s multibillion-dollar recreational marijuana industry in states like Massachusetts and New York.^[152]

Since 2014, numerous US states have passed “Right to Try” laws protecting access to unapproved therapies. In some ways, these laws are analogous to early state efforts to decriminalize marijuana. Right to Try laws have always been criticized on the grounds that they violate federal preemption and will therefore be ignored and abrogated by the FDA—the very criticism that greeted early state laws decriminalizing marijuana. Nonetheless, both Right to Try and state-legal marijuana exist in a gray area between law and politics. In both cases, federal agencies have been hesitant to intercede in state frameworks authorizing theoretically federally illegal activity.

While no one reliable database tracks state Right to Try usage, it is likely that—over the past decade—at least 200-300 Americans have received treatments under these laws without any instance of FDA preemption. This estimate is usually shared by innovators and policymakers familiar with the field. One prolific provider of Right to Try treatments, Texas physician Ebrahim Delpassand, has used Texas’ Right to Try law to treat 78 patients with radioligand therapy.^[153]

In the years that the authors have discussed and advocated for expanded access frameworks, no stakeholder they have spoken with has ever been able to identify a single instance in which the FDA engaged in preemption in response to a patient receiving a state-legal Right to Try treatment. While the FDA has so far been loath to codify this practice of nonenforcement, or even acknowledge it in writing, several FDA officials have verbally acknowledged this reality.

Most Right to Try laws have nonetheless been limited, weak, and ineffective. A new wave of Right to Try laws—namely those in Montana, Florida, and New Hampshire—could allow frontier therapies to be offered at commercial scale. By formally protecting these state frameworks, a Cole Memorandum for biotech would allow America to replicate certain features of CTNs, IITs, and green channel pathways.

Florida’s 2025 “stem cell law,” known as SB 1768, allows patients to be treated with federally unapproved stem cell therapies, subject to rigorous statutory guardrails around stem cell quality, for reasons including wound-care and pain management.^[154] While relatively limited in scope, Florida’s law is notable for its ability to rapidly create a visible, commercially scalable ecosystem around a Right to Try law. The Florida Board of Medicine even has an “SB 1768 Stem Cell Therapy Workgroup” focused on implementing the law.^[155]

Montana’s renowned Right to Try law is perhaps the most theoretically promising of these new frameworks. The law partially replicates the CTN or IIT pathway by authorizing a state health agency to license “experimental treatment centers” to commercialize post-Phase 1 therapies to any patient whose doctor is willing to prescribe them.^[156] To win state-level licensing, these centers must have a qualified scientific review board—effectively an IRB—which reviews and approves each therapy. The Montana framework falls short of the Chinese or Australian system only insofar as the research it generates will ordinarily fall outside the federal approval framework and therefore not shape domestic insurance coverage.

New Hampshire’s law is—with some qualifications—essentially limited in scope to patients with a discrete terminal illness. For patients in that category, however, New Hampshire has the strongest protections in the country,^[157] including a more robust civil liability waiver than any other state,^[158] a right to injunctive relief against regulators, and unique protections around remote prescreening for relevant clinical trials. New Hampshire’s law also allows patients to receive therapies that have not passed Phase 1 trials within certain parameters.

The “Live Free or Die” state is also home to a substantial pro-biotech movement. In 2026, advocates sought to position New Hampshire as a national hub for frontier therapies by passing both Florida- and Montana-style laws—a campaign endorsed by the Governor and New Hampshire House but opposed and largely stopped, for now, by New Hampshire’s State Senate.^[159]

A Cole Memorandum could allow these state-based ecosystems to scale—unleashing substantial industries in pro-innovation states and fostering competition between them. The original Cole Memorandum already sets forth the broad contours for regulators to follow. While reserving its enforcement prerogatives, the FDA can provide written encouragement that good-faith compliance with a robust state Right to Try law will not be met with federal enforcement action. This is perhaps

the most immediately achievable of the four proposed reforms because—like the Cole Memo itself—it would recognize a decade-old *de facto* FDA practice while expanding on already established state law frameworks.

2. Reclassify Individualized Biologics as Medical Practice

The single highest-impact reform that regulators could undertake would be for HHS or the FDA to issue guidance reclassifying individualized biologics—perhaps within certain contours—as a form of medical practice. Bespoke gene therapy would then be reinterpreted as a kind of gene surgery, with varieties of gene therapy classified as therapeutic techniques governed by institutional review boards rather than full FDA IND requirements. Replicating many benefits of CTN and IIT, this would remove the scalability barrier for personalized therapies and could help secure US dominance over China.^[160]

This would not, as some assume, unleash a prewar “Wild West” upon American patients. Medical practice in the US is far from unregulated: it is governed by state licensing boards, malpractice liability, state agency regulation, and state statute. FDA guidance reclassifying individualized therapies could also require that new gene-therapy techniques be supervised by qualifying IRBs as in Australia or China. For individualized biologics, a system of multi-phase approval controlled by federal regulators is an unnecessary fifth or sixth layer amounting to a *de facto* ban on life-saving innovation.

By categorizing IVF as a form of medical practice rather than a biologic requiring premarket approval, the FDA has largely allowed IVF to be governed by state licensing, professional standards, tort liability, and clinic-level review. The result has been a mature and broadly safe field. Reclassifying individualized biologics as therapeutic techniques would offer innovations such as bespoke gene therapy the same treatment the United States already gives to assisted reproduction.

3. A Sua Sponte Green Channel

The United States should create a sua sponte, or regulator-driven, green channel pathway that primarily utilizes real-world evidence as well as other evidence short of randomized controlled trials—including mechanistic rationale, surrogate endpoints, single-arm results, foreign approvals—where that evidence makes a therapy’s benefit reasonably likely.^[161] This proposal could be pursued and implemented in two phases—one circumventing Congressional action and one requiring it.

In an initial phase, the FDA could issue nonenforcement guidance modeled on its existing Interim Policy regarding bulk drug substances. Entrepreneurial regulators could take up therapies whose available evidence makes their benefit reasonably likely—either on industry nomination or *sua sponte*—and then simply list them in an expanded Interim Policy as quasi-approved in the FDA’s enforcement discretion.

While this proposal may sound radical, this hesitation is best understood as a reflection of path-dependence. The FDA’s Interim Policy on bulk drug substances, China’s green channel pathways, and other models already show there is nothing inherently anarchic or unsafe about regulator-driven, therapy-by-therapy approval. Among other benefits, this system could form the beginning of a commercial pathway for therapies intended to be health-enhancing rather than disease-treating—a category of therapies that the FDA paradigm is not well-suited to address.

Ultimately, Congress could formalize this green channel in federal law. One way or another, this pathway would require substantial presidential emphasis on hiring pro-innovation agency personnel from frontier biotech. It would not, by itself, solve the insurance problem, but it would directly address the approval bottleneck.

4. A Single Federal Appeals Court for Drugs and Biologics

Finally, Congress should take a page from patent law and establish a single federal appeals court for drugs and biologics—staffed by judges with at least some subject matter expertise in biotechnology. The absurd outcome in *US v. Regenerative Sciences* is a reminder that some federal judges may not be qualified to protect medical practice from regulatory overreach. The present-day constitutional law of interstate commerce was crafted to help the federal government control wheat production—not to accommodate AI-driven gene editing.

The Administrative Conference of the United States has identified three criteria that justify creating a specialized court for review of a particular administrative program: a consistently large volume of cases whose diversion would meaningfully relieve the generalist courts of appeals, the predominance of case-specific factual issues—or of scientific and technical issues demanding decisionmaker expertise—and a particular need for uniformity in the agency’s administration of the program.^[162]

The second ACUS criterion—the predominance of technical or scientific issues requiring specialized expertise—is particularly strong evidence of the need for a biotech-specialist appeals court. Congress created the Federal Circuit in 1982 in part because patent cases turned on technical subject matter that generalist judges were poorly positioned to adjudicate consistently across circuits.^[163] Biotech review presents the same structural problem.

If technical complexity justified specialized review of patent cases, it also justifies specialized review of decisions that determine patients' access to treatment.

Conclusion

America's precarious position in biotech is a self-inflicted problem. Other nations may surpass us largely because they have declined to force every advance in medicine into the midcentury artifact of America's one-size-fits-all system.

Comparison among the nations of the bio-tetrarchy shows that the American framework is not a necessary bulwark against the "Wild West" or "Frankenstein's Monster," but a construct of arbitrary path dependence that other nations already improved upon. Keeping the biotech frontier in America will demand a revolutionary willingness to wrangle or reform the system—but the levers are within reach through realistic reforms.

America already possesses every advantage—capital, talent, institutions—save one: the imagination to rethink and reform its regulatory paradigm. The coming wave of individualized therapy will, sooner or later, reach patients around the world. The only question is whether it comes to America first.

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- Regenerative Therapy Ethics Review Committee, which grants full, provisional, or research approval or none; a companion Board receives applications, issues the written authorization to begin, and is charged with “encouraging the advancement of medical tourism and translational sciences in the Field.” The Act imposes no multi-phase trial requirement, and it reaches non-disease indications directly, defining “longevity” as “a long and healthy duration of individual life as measured by the capability to survive beyond the species-specific average age of death, the individual’s ability to live past their life expectancy at birth.” Longevity and Regenerative Therapies Act, 2024, No. 51 of 2024, §§ 2, 8(b), 12–14 (Bah.), https://laws.bahamas.gov.bs/cms/images/LEGISLATION/PRINCIPAL/2024/2024-0051/2024-0051_1.pdf. ↑
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48. In this way, Chinese gatekeepers sometimes have more in common with an ARPA-H program manager than an FDA regulator. ↑
49. Elisabeth A. Cawthon, *Thalidomide Tragedy Prompts Passage of the Kefauver-Harris Amendment*, EBSCO Rsch. Starters (2023), <https://www.ebsco.com/research-starters/history/thalidomide-tragedy-prompts-passage-kefauver-harris-amendment>. ↑
50. C.T.G. King & F.J. Kendrick, Teratogenic Effects of Thalidomide in the Sprague Dawley Rat, 280 Lancet 1116 (1962), [https://doi.org/10.1016/S0140-6736\(62\)90822-X](https://doi.org/10.1016/S0140-6736(62)90822-X). ↑
51. Suzanne White Junod, FDA and Clinical Drug Trials: A Short History, 10, U.S. Food & Drug Admin., <https://www.fda.gov/media/110437/download> (last visited June 26, 2026) (Mandatory efficacy testing was first required by a 1962 statute, while the “phase” system was formalized by 1963 regulations). ↑
52. Lonsdale, *supra* note 4. ↑
53. See, e.g., Myrisha S. Lewis, *Regulating Conception: Science, Politics, and Reproductive Genetic Innovation* 65 (2026). ↑
54. Id. at 26. To say nothing of private professional and industry norms. ↑
55. *What Peptides Are Becoming Legal in 2026*, Open Loop Health (last visited June 29, 2026), <https://openloophealth.com/blog/what-peptides-are-becoming-legal-2026>. ↑
56. FDA, *Bulk Drug Substances Nominated for Use in Compounding Under Section 503A*, <https://www.fda.gov/drugs/human-drug-compounding/bulk-drug-substances-used-compounding-under-section-503a-fdc-act> (last visited June 29, 2026). ↑
57. Lewis, *supra* note 53, at 67. ↑

58. InterMune's Esbriet (pirfenidone), for example, was approved in Japan in 2008 to treat idiopathic pulmonary fibrosis. Although the FDA's own Advisory Committee recommended it for approval in 2010, its US approval was delayed until 2014 solely because the FDA requested a US Phase 3 efficacy trial. Press Release, InterMune, Inc., FDA Advisory Committee Recommends Approval of InterMune's Esbriet® (pirfenidone) for Idiopathic Pulmonary Fibrosis (Mar. 9, 2010), <https://www.prnewswire.com/news-releases/fda-advisory-committee-recommends-approval-of-intermunes-esbriet-pirfenidone-for-idiopathic-pulmonary-fibrosis-87151342.html>; InterMune, Inc., Current Report (Form 8-K), Exhibit 99.2, Risk Factors (Mar. 12, 2014), <https://www.sec.gov/Archives/edgar/data/1087432/000119312514095563/d691767dex992.htm>. ↑
59. FDA, *FDA at a Glance 2 (Jan. 2026) (FY2025 budget)*, <https://www.fda.gov/media/154548/download>. ↑
60. 21 C.F.R. §§ 170.225–170.260. ↑
61. *Post-market Determinations that the Use of a Substance is Not GRAS*, U.S. Food & Drug Admin. (content current as of May 8, 2025), <https://www.fda.gov/food/generally-recognized-safe-gras/post-market-determinations-use-substance-not-gras>. ↑
62. *GRAS Self-Affirmation for Food Ingredients: To Be or Not to Be?*, Beveridge & Diamond (last visited June 29, 2026), <https://www.bdlaw.com/publications/gras-self-affirmation-for-food-ingredients-to-be-or-not-to-be/>. ↑
63. Australia and China are also more rigorous regulators of food additives than the United States. In contrast to the GRAS system, Australia, China, and the EU all subject food additives to regulator-gatekept premarket approval systems. Ying Niu, Yongxiang Fan & Jiyue Zhang, Progress and Challenge in the Risk Management of Food Additives, 88 J. Food Prot. 100607 (2025) (published online Aug. 26, 2025; issue dated Sept. 24, 2025), <https://www.sciencedirect.com/science/article/pii/S0362028X25001590>. The Sino-Australian model therefore represents a kind of common sense framework in contrast to FDA path dependence: food additives are subject to *ex ante* regulator gatekeeping while biologics, which patients need to survive, are hastened through IRB-gatekeeping and thereby entrusted more heavily towards *ex post facto* remedies. ↑
64. 21 C.F.R. § 170.3(i), <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-170/subpart-A/section-170.3>. The regulation adds explicitly that “It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance.” *Id.* This is a notable contrast with the drugs and biologics context, in which any similar statement is seen as accelerationist and anarchic. The FDA chose to write an explicit acknowledgment of irreducible scientific uncertainty into the safety standard for food: the drug and biologic provisions contain nothing of the kind. Interestingly, China and the FDA disapprove food additives at similar rates; ~20% of US GRAS notifications are “withdrawn” by notifiers, while ~20% of additives submitted to Chinese regulators are given explicit administrative disapproval. CIRS, *Analysis on the Application and Approval of New Food Additives in 2024*, CIRS Group (Jan. 24, 2025), <https://www.cirs-group.com/en/food/analysis-on-the-application-and-approval-of-new-food-additives-in-2024>. Unlike in China or Australia, however, an additive with a withdrawn GRAS notification—or even a rare explicit disapproval—can be lawfully sold as GRAS in the US in the absence of *post-market adjudication*. *Post-market Determinations that the Use of a Substance is Not GRAS*, U.S. Food & Drug Admin. (content current as of May 8, 2025), <https://www.fda.gov/food/generally-recognized-safe-gras/post-market-determinations-use-substance-not-gras>. ↑
65. 21 C.F.R. pt. 182, subpt. D, <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-182/subpart-D?toc=1> (last visited June 29, 2026). ↑
66. *Hungry Jack Instant Mashed Potatoes*, Kroger (last visited June 29, 2026), <https://www.kroger.com/p/hungry-jack-instant-mashed-potatoes/0001114087102>. ↑
67. *Totino's Pizza Rolls Pepperoni Pizza Snacks*, Fresh Grocer (last visited June 29, 2026), <https://www.thefreshgrocer.com/sm/pickup/rsid/2000/product/totinos-pizza-rolls-pepperoni-pizza-snacks-15-count-75-oz-id-00042800005830> (Totino's is a General Mills product). ↑
68. *Jack Link's Original Beef Sticks*, Jay C Food Stores (last visited June 29, 2026), <https://www.jaycfoods.com/p/jack-link-s-original-beef-sticks/0001708287400>. ↑

69. Yan et al., *supra* note 6, at 2631 (reporting 256 new drug approvals in China against 243 in the United States, 191 in the European Union, and 187 in Japan over 2019–2023). ↑
70. Yan et al., *supra* note 6, at 2633 (*China–U.S.* approval-date gap narrowing from 735 to 384 days, and the *China–E.U.* gap from 795 to 132 days, after 2021). ↑
71. Goldman Sachs, *supra* note 7 (“About a quarter of innovative drug candidates now under active development originate from China,” and 46% of new molecules entering human trials in the first half of 2025 came from Chinese companies, up from roughly 17% a decade earlier). ↑
72. *Id.* (Chinese biopharma responsible for roughly 70% of global antibody-drug-conjugate development and about 60% of bispecific antibodies over the prior two and a half years). ↑
73. Gale, *supra* note 9 (188 versus 99 registered CAR-T leukemia studies; 234 versus 159 for lymphoma; 64 versus 55 for plasma-cell myeloma). ↑
74. *Id.* Gale attributes the disparity in part to “the speed at which a new study is approved in China versus the United States,” and observes that many Chinese trials use CAR-T cells produced locally at a medical center or in collaboration with a small biotechnology company—uncommon in the United States, where FDA approval “requires large, complex, expensive clinical trials.” ↑
75. Bruce Liu et al., *supra* note 10 (reporting direct per-patient cost of approximately \$69,000 in the United States versus \$25,000 in China for Phase 3 non-small-cell lung cancer trials). ↑
76. David Cyranoski, *Chinese Scientists to Pioneer First Human CRISPR Trial*, *Sci. Am.* (July 21, 2016) (reproduced from *Nature*), <https://www.scientificamerican.com/article/chinese-scientists-to-pioneer-first-human-crispr-trial/>; see You Lu et al., *Safety and Feasibility of CRISPR-Edited T Cells in Patients with Refractory Non-Small-Cell Lung Cancer*, 26 *Nature Med.* 732 (2020), <https://www.nature.com/articles/s41591-020-0840-5> (NCT02793856; ethics approval July 6, 2016; first patient dosed Oct. 28, 2016). ↑
77. Edward A. Stadtmauer et al., *CRISPR-Engineered T Cells in Patients with Refractory Cancer*, 367 *Science* eaba7365 (2020) (three U.S. patients dosed in 2019 following review by an NIH advisory panel, the FDA, and the university institutional review board). ↑
78. See Sheryl Gay Stolberg, *The Biotech Death of Jesse Gelsinger*, *N.Y. Times Mag.* (Nov. 28, 1999), <https://www.nytimes.com/1999/11/28/magazine/the-biotech-death-of-jesse-gelsinger.html> (eighteen-year-old volunteer died Sept. 17, 1999, of an immune reaction to an adenoviral vector); *Clinical Trials Put on Hold at Gene-Therapy Lab*, *The Pennsylvania Gazette* (Mar. 2, 2000), <https://thepenngazette.com/clinical-trials-put-on-hold-at-gene-therapy-lab/> (reporting FDA’s January 2000 suspension of trials at Penn’s Institute for Human Gene Therapy). ↑
79. Min Liang, *Oncorine, the World First Oncolytic Virus Medicine and Its Update in China*, 18 *Current Cancer Drug Targets* 171 (2018), <https://pubmed.ncbi.nlm.nih.gov/29189159/> (H101, developed by Shanghai Sunway Biotech, approved by the SFDA in November 2005 for nasopharyngeal carcinoma in combination with chemotherapy, with GMP certification in August 2006; Phase 3 response rate of roughly 79% for H101 plus chemotherapy versus 40% for chemotherapy alone). ↑
80. See *id.* (E1B-55kDa deletion confers selective replication in p53-deficient tumor cells). The analogous U.S. construct, ONYX-015, was never approved by the FDA. ↑
81. Wei-Wei Zhang et al., *The First Approved Gene Therapy Product for Cancer Ad-p53 (Gendicine): 12 Years in the Clinic*, 29 *Hum. Gene Therapy* 160 (2018), <https://pubmed.ncbi.nlm.nih.gov/29338444/>; *China Approves First Gene Therapy*, 22 *Nature Biotech.* 3 (2004), <https://pmc.ncbi.nlm.nih.gov/articles/PMC7097065/> (SFDA drug license issued Oct. 16, 2003; GMP clearance and commercial launch 2004; recombinant adenovirus delivering wild-type p53 for head and neck squamous cell carcinoma). ↑

82. Zhang et al., *supra* note 81 (based on twelve years of commercial use in more than 30,000 patients and more than 30 published clinical studies, “Gendicine has exhibited an exemplary safety record”; “[n]o serious adverse events have been reported, except for vector-associated transient fever, which occurred in 50-60% of patients”). ↑
83. Introgen Therapeutics, Inc., Current Report (Form 8-K), Item 8.01 & Ex. 99.1 (Sept. 2, 2008), SEC accession No. 0001157523-08-007215, <https://www.sec.gov/Archives/edgar/data/1018710/000115752308007215/a5767734.htm> (FDA declined to file the Advexin biologics license application as insufficiently complete); Introgen Therapeutics, Inc., Current Report (Form 8-K), Item 1.03 (Dec. 4, 2008), SEC accession No. 0000950134-08-021653, <https://www.sec.gov/Archives/edgar/data/1018710/000095013408021653/d65452e8vk.htm> (Chapter 11 petitions filed Dec. 3, 2008). ↑
84. See *Cancer Patients Travel to China for Gene Therapy*, Progress Educ. Tr. (2004), <https://www.progress.org.uk/cancer-patients-travel-to-china-for-gene-therapy/> (reporting that of roughly 400 patients then treated with Gendicine, about 20 came from abroad); *China Reports Approval of World’s First Gene Therapy*, Oral Cancer News (Mar. 25, 2009), <https://oralcancernews.org/wp/china-reports-approval-of-world%E2%80%99s-first-gene-therapy/> (“hundreds of patients abroad have traveled to China so far to receive the drug”). Both are trade or advocacy sources rather than peer-reviewed literature, and their estimates describe different periods rather than necessarily conflicting counts of one cohort; precise cumulative figures are unavailable. See also *Chinese Gene Therapy Offers Hope to Terminally Ill Cancer Patients*, Sunday Telegraph (July 4, 2004), <https://www.telegraph.co.uk/news/worldnews/asia/china/1466158/Chinese-gene-therapy-offers-hope-to-terminally-ill-cancer-patients.html> (contemporaneous reporting on foreign patients seeking treatment, identified in the Progress Educational Trust article’s source list). ↑
85. The authors are grateful to Yiwei She for her assistance in understanding the Chinese regulatory system. ↑
86. Provisions for Drug Registration (药品注册管理办法), SAMR Order No. 27 (promulgated Jan. 22, 2020, eff. July 1, 2020), ch. IV, arts. 59–75, https://english.nmpa.gov.cn/2022-06/30/c_785628_6.htm; <https://sjfg.samr.gov.cn/law/file/pdf/3235243/1663496603982.pdf> (Chinese text). See Regulations for the Implementation of the Drug Administration Law (中华人民共和国药品管理法实施条例), State Council Order No. 828 (revised Jan. 16, 2026, eff. May 15, 2026), art. 15, <https://policy.mofcom.gov.cn/claw/clawContent.shtml?id=104716>. The 2020 provisions require applications and agency review; art. 61 allows staged data submission and agency guidance, arts. 63–67 provide conditional approval and confirmatory-study requirements, arts. 68–71 address priority review, and arts. 72–75 address special approval. These procedures do not establish unrestricted sua sponte marketing approval. ↑
87. Yan et al., *supra* note 6, at 2635–2636 (describing the four accelerated procedures as a green channel for new drug research and development). ↑
88. See State Council, *Opinions on Comprehensively Deepening the Reform of Regulation of Drugs and Medical Devices* (Dec. 2024), https://english.nmpa.gov.cn/2025-03/25/c_1080973.htm. ↑
89. Bruce Liu et al., *supra* note 10 (“[I]n early April of 2025, the Beijing municipal government announced ‘Several Measures to Support the High-Quality Development of Innovative Medicines’; investigational drug applications now processed within thirty working days, down from sixty”). ↑
90. FDA, Right to Try Annual Reporting Summary, <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try-annual-reporting-summary> (last visited Oct. 10, 2026). The reported figures are twelve eligible drugs or biological products for 2018–2022, four for 2023, and five for 2024, totaling twenty-one product uses across reporting periods; they are not patient or dose counts, and a product may recur across years. The summary additionally reports six products for 2025. Sponsors report individual-patient counts to FDA on Form FDA 5023, <https://www.fda.gov/media/164463/download>, but the public summary does not provide those counts. A published SITOIGANAP cohort included twenty-one treated patients under US Right to Try or foreign compassionate-use pathways; it does not establish the national US patient total. See Daniela A. Bota et al., A Prospective, Cohort Study of SITOIGANAP to Treat Glioblastoma When Given in Combination With Granulocyte-Macrophage Colony-Stimulating Factor/Cyclophosphamide/Bevacizumab/Nivolumab or Granulocyte-Macrophage Colony-Stimulating Factor/Cyclophosphamide/Bevacizumab/Pembrolizumab in Patients Who Failed Prior Treatment With Surgical Resection, Radiation, and Temozolomide, 12 *Frontiers in Oncology* 934638, 3–4 (2022), <https://doi.org/10.3389/fonc.2022.934638>. ↑

91. Prasad & Makary, *supra* note 2. ↑
92. Lu Xu et al., *The Role of Investigator-Initiated Trials in Advancing Cell and Gene Therapy Under China's Dual-Track Regulatory System*, 12 Heliyon e44902 (2026) (cell and gene therapies regulated either as biologics by the NMPA, requiring an IND and a biologics license application, or as medical technologies by the National Health Commission, proceeding through investigator-initiated trials on institutional ethics-committee approval and a filing with health authorities, without central premarket approval; non-IND IITs outnumber IND projects by a factor of 14.19, or 823 to 58, cumulatively from 2000 to 2021). ↑
93. Liu et al., *supra* note 10 ("Many cell and gene therapies have been leveraging the IIT for fast proofs of concept"). ↑
94. Gail Dutton, *China Sets Framework for Advanced Therapeutic Development*, GEN (June 18, 2026), <https://www.genengnews.com/topics/translational-medicine/china-sets-framework-for-advanced-therapeutic-development/>. See also Nat'l Health Comm'n, Guidance List for Filing Clinical Research on New Biomedical Technologies (ver. 1), §§ I, V, <https://file.ciopharma.com/Public/Uploads/Oss/20260506/8622f8f3c6fcf133b1bf6739509f63c710fe0d30.pdf> (last visited Oct. 12, 2026) (listing gene-therapy and brain-computer-interface technologies). ↑
95. State Council Order No. 818, arts. 11, 14–15, 20, 29–34 (promulgated Sept. 28, 2025, effective May 1, 2026) (China), <https://www.nhc.gov.cn/wjw/xwdt/202510/0f476b3eceab4cb0b4601a3ec00971c8.shtml> (eligible hospitals; academic and ethical review; research filing; prohibition on research-related charges; separate approval and permitted charges for clinical translation). ↑
96. Nat'l Health Comm'n, Work Specifications for the Approval of Clinical Translation and Application of New Biomedical Technologies (Trial Implementation), Notice No. 13 of 2026, arts. 3–4, 6–7, 18–19 (issued Apr. 30, 2026, effective May 1, 2026) (China), <https://www.nhc.gov.cn/qjjys/c100016/202604/6d64fdc552ee49f4abba44831d189201.shtml>. ↑
97. Work Specifications for the Approval of Clinical Translation and Application of New Biomedical Technologies (Trial Implementation), art. 17 (2026) (China); State Council Order No. 818, arts. 29–31 (2025) (China), <https://www.nhc.gov.cn/wjw/xwdt/202510/0f476b3eceab4cb0b4601a3ec00971c8.shtml>. ↑
98. Brendan Borrell, *Exclusive: Death of Girl in Chinese Gene-Editing Trial Was Never Made Public*, Science (July 23, 2026), <https://www.science.org/content/article/exclusive-death-girl-chinese-gene-editing-trial-was-never-made-public>. ↑
99. *Id.* ("Philippe Campeau, a medical geneticist at the University of Montréal who helped identify the syndrome's genetic basis in 2018, says people with the mutation often have a normal life expectancy, but their symptoms vary widely. Most have slightly larger than normal heads, and about two-thirds have intellectual deficits. Moderate to severe cases may be nonverbal, suffer from seizures and heart problems, and have fluid-filled voids in their heads... Mei sat on the milder end of the gradient, but Linda soon quit her job to devote her energy to their only child."). ↑
100. *Id.* ↑
101. *Id.* ↑
102. *Id.* ("Another potential concern, however, emerged about 1 month before Mei was treated: the final conclusions of a primate toxicology study conducted at PriMed. The company's report, dated 17 February 2025, concluded all four monkeys that received the [AAV] therapy, whether at low or high doses, developed moderate to severe liver damage... One monkey, which received a high dose of the viruses, also showed kidney damage."). ↑
103. *Id.* ↑
104. See Cyranoski, *supra* note 76; Gale, *supra* note 9. The characterization of the 2016 trial as an investigator-initiated study is an inference from these sources rather than a label the trial bore at the time; the National Health Commission's formal measures governing investigator-initiated cell-therapy research were not issued until 2021, so the 2016 trial proceeded under a less codified version of the same hospital-ethics-committee logic. *But cf.* Simone McCarthy, *Girl's Undisclosed*

Death in Gene-Editing Trial Raises Red Flags in Booming Chinese Industry, CNN (July 30, 2026), <https://www.cnn.com/2026/07/30/china/china-death-gene-editing-trial-intl-hnk> (“These small-scale clinical trials generally undergo less oversight than the traditional approval pathway for a green light. Similar models exist in other countries and are seen as important to accelerating breakthroughs and administering life-saving treatments especially for rare diseases, where there is little commercial incentive for research. But they may also come with risks.”). ↑

105. Dutton, *supra* note 94. ↑

106. *Four Takeaways from Our Investigation into a Hidden Gene-Editing Death*, Science (July 23, 2026), <https://www.science.org/content/article/four-takeaways-our-investigation-hidden-gene-editing-death>. ↑

107. Testimony of Bess Stillman, M.D., on H.B. 701 Before the H. Comm. on Health, Human Servs. & Elderly Affairs, 2025 Leg., Reg. Sess. (N.H. 2025), <https://www.nhcornerstone.org/wp-content/uploads/2025/03/Dr.-Bess-Stillman-HB-701-Testimony.pdf>. ↑

108. Alina Wang, *Chinese Girl Dies After Experimental Gene-Editing Therapy Amid Cover-Up Allegations*, Vision Times (July 31, 2026), <https://www.visiontimes.com/2026/07/31/chinese-girl-dies-after-experimental-gene-editing-therapy-amid-cover-up-allegations.html>. ↑

109. Anna Lene Seidler et al., *The Changing Landscape of Clinical Trials in Australia*, 219 Med. J. Austl. 192, 192–196 (2023), <https://www.mja.com.au/journal/2023/219/5/changing-landscape-clinical-trials-australia> (“From 2006 to 2020, over 18 000 trials recruiting participants in Australia were registered”; Australian per-capita trial activity exceeds that of France, Germany, and the United States). See also Australian Trade and Investment Commission, *Life Sciences in Australia: Industry Capability Report 11*, <https://international.austrade.gov.au/content/dam/austrade-assets/international/documents/reports/health-and-life-sciences/life-sciences-australia-industry-capability-report.pdf> (last visited Oct. 10, 2026) (commercially sponsored trial initiation per capita and Phase 1 trial rankings). ↑

110. Therapeutic Goods Administration, *Clinical Trial Notification (CTN) Scheme*, <https://www.tga.gov.au/products/unapproved-therapeutic-goods/access-pathways/clinical-trials/clinical-trial-notification-ctn-scheme> (last visited June 29, 2026); see Therapeutic Goods Act 1989 (Cth) ss 18(1), 32CA(2), 41HA; Therapeutic Goods Regulations 1990 (Cth) sch 5A item 3. ↑

111. Nat’l Inst. of Allergy & Infectious Diseases, *Clinical Research Regulation for Australia*, ClinRegs, <https://clinregs.niaid.nih.gov/country/australia> (last visited June 29, 2026) (under the CTN system “the Therapeutic Goods Administration (TGA) does not review or evaluate any data relating to the clinical trial”; the human research ethics committee assesses scientific validity, risk, and ethical acceptability). ↑

112. Schell, *supra* note 43 (quoting Tina Soulis, Founder, Alithia Life Sciences). The interview describes acknowledgment within two weeks and frequently within days. See TGA, *Clinical Trial Notification (CTN) Scheme*, *supra* note 110 (recruitment does not require receipt of TGA’s acknowledgment). ↑

113. *Conducting Clinical Trials in Australia*, Syner-G BioPharma, <https://synergiopharma.com/blog/conducting-clinical-trials-in-australia/> (last visited June 29, 2026) (start-up of approximately 6–12 weeks); see also Schell, *supra* note 43 (ethics-committee comments within roughly 48 hours; most projects moving from final protocol to first patient in two to three months). ↑

114. Schell, *supra* note 43 (quoting Soulis). For first-in-human studies of certain Class 4 biologicals—typically cell and gene therapy products with no prior clinical use—the more demanding Clinical Trial Approval (CTA) pathway applies, under which the TGA reviews product-level data before ethics approval. See Therapeutic Goods Administration, *Review of the Clinical Trial Approval (CTA) Scheme*, <https://www.tga.gov.au/products/unapproved-therapeutic-goods/access-pathways/clinical-trials/review-clinical-trial-approval-cta-scheme> (last visited June 29, 2026). ↑

115. Austl. Tax'n Off., Rates of R&D Tax Incentive Offset, <https://www.ato.gov.au/businesses-and-organisations/income-deductions-and-concessions/incentives-and-concessions/research-and-development-tax-incentive-and-concessions/research-and-development-tax-incentive/rates-of-r-d-tax-incentive-offset> (last visited June 29, 2026) (refundable offset equal to the company tax rate plus an 18.5-percentage-point premium for eligible entities with aggregated turnover below AUD \$20 million). ↑
116. *Federal Budget 2026: R&D Tax Changes*, Treadstone (last visited June 29, 2026), <https://www.treadstone.com.au/federal-budget-2026-rdtax-changes/>. ↑
117. The 43.5% rate and AUD \$20 million turnover threshold apply to the 2025–26 and 2026–27 income years. Changes announced in the May 2026 Federal Budget are proposals intended to apply from July 1, 2028, subject to legislation: a refundable offset of up to 48%, eligibility restricted to companies operating fewer than ten years with turnover below AUD \$50 million, and a 1.5% non-refundable intensity threshold. See Treadstone, *Budget 2026: R&D Tax Incentive Changes Explained*, <https://www.treadstone.com.au/federal-budget-2026-rdtax-changes/> (last visited Oct. 10, 2026) (identifying the changes as proposals requiring legislation). ↑
118. See Letter of Intent between RespireRx Pharmaceuticals Inc. / ResolutionRx Ltd. and Radium Capital, Ex. 99-2 (SEC EDGAR, filed Feb. 2023), <https://www.sec.gov/Archives/edgar/data/849636/000149315223003248/ex99-2.htm> (Radium advancing up to 80% of the anticipated refund at a 16% annual interest rate, secured against the R&D tax refund). ↑
119. FDA, *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions*, Guidance for Industry and FDA Staff (Mar. 2012), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-acceptance-foreign-clinical-studies-not-conducted-under-ind-frequently-asked-questions>; 21 C.F.R. § 312.120 (foreign clinical studies not conducted under an IND may support an IND or marketing application if they satisfy the applicable requirements, including good clinical practice, independent ethics-committee review, and informed consent). ↑
120. Frost & Sullivan, *Australia: Preferred Destination for Early-Phase Clinical Trials* (Novotech white paper), <https://www.frost.com/growth-opportunity-news/australia-preferred-destination-early-phase-clinical-trials/> (last visited June 29, 2026) (Australia approximately 28% less costly than the United States before incentives and approximately 60% less costly after). ↑
121. Russell Hayward, *How an Australia-First Strategy Cut 63% From Our R&D Spend*, Clinical Leader (July 10, 2025), <https://www.clinicalleader.com/doc/how-an-australia-first-strategy-cut-from-our-r-d-spend-0001>. Hayward, the chief executive of Dallas-based Etira, attributes the saving to stacked factors including a favorable currency exchange, so the figure should not be read as a pure regulatory or tax saving. ↑
122. The authors are grateful to Pedro Henrich for his assistance in understanding Japan's regulatory framework for biologics. ↑
123. Pharmaceuticals and Medical Devices Agency, *Regenerative Medical Products*, <https://www.pmda.go.jp/english/review-services/reviews/0003.html> (last visited June 29, 2026) (defining a regenerative medical product as processed—more than minimally manipulated—live human or animal cells intended to reconstruct, repair, or form the structures or functions of the human body, or to treat or prevent disease, and including gene therapy). The category was created by the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act), effective Nov. 25, 2014. ↑
124. Sipp & Okano, *supra* note 47. ↑
125. Hayase Hakariya et al., *Japan's Conditional/Time-Limited Early Approval System in Regenerative Medicine: A Case Study of Rise and Falls of Autologous Skeletal Myoblast Sheets*, 117 Clin. Pharmacology & Therapeutics 1171 (2025), <https://pmc.ncbi.nlm.nih.gov/articles/PMC11993280/>. ↑
126. Mototsugu Tanaka et al., *Conditional Early Approval for New Drug Applications in Japan: Current and Emerging Issues*, 16 Clin. & Translational Sci. 1289 (2023), <https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.13536>. ↑

127. Office of Pharmaceutical Industry Research, Why Do New Drugs Reach Patients 60 Days After Approval?—The Birth of the 60-Day Rule, Its Current Status, and Its Future, §§ 1–4, <https://en.jpma.or.jp/opir/news/066/11.html> (last visited Oct. 10, 2026) (describing national health-insurance price listing after regulatory approval and the standard 60–90-day administrative period). ↑
128. Naoki Ikegami et al., Japanese Universal Health Coverage: Evolution, Achievements, and Challenges, 378 *Lancet* 1106 (2011), [https://doi.org/10.1016/S0140-6736\(11\)60828-3](https://doi.org/10.1016/S0140-6736(11)60828-3) (describing universal coverage achieved in 1961 and a uniform payment system across approximately 3,500 insurers). ↑
129. World Health Systems Facts, Japan: Healthcare Coverage and Access, <https://healthsystemsfacts.org/national-health-systems/bismarck-model/japan/japan-health-system-coverage/> (last visited June 29, 2026) (the national fee schedule “uses a single price without any regional adjustments”); see also PMDA, Japan’s NHI Drug Price System, <https://www.pmda.go.jp/files/000248690.pdf>. Prices are set centrally by the Central Social Insurance Medical Council (Chuihyo), which lists new drugs four times yearly. ↑
130. Office of Pharmaceutical Industry Research, *supra* note 127, §§ 2–4 (the standard administrative period is within sixty days in principle or ninety days at the latest; 6.6% of the FY2015–FY2021 sample was listed late). The sample excludes regenerative medical products, so its timing figures should not be generalized to all such products. On the separate conditional and time-limited approval scheme for regenerative medical products, see Shinichi Noda et al., Regulatory Advancements in Japan’s Conditional and Time-Limited Approval Scheme for Regenerative Medical Products: The First Guidance on the Approval Scheme and the Second Review for Full Approval of the First Conditional and Time-Limited Approved Cellular Product, *HeartSheet*, 27 *Cytotherapy* 700 (2025), <https://doi.org/10.1016/j.jcyt.2025.02.010>. ↑
131. Masataka Hasegawa et al., *Formal Implementation of Cost-Effectiveness Evaluations in Japan: A Unique Health Technology Assessment System*, 23 *Value Health* 43 (2020), [https://www.valueinhealthjournal.com/article/S1098-3015\(19\)35170-8/fulltext](https://www.valueinhealthjournal.com/article/S1098-3015(19)35170-8/fulltext). ↑
132. FDA approval and insurer coverage are separate decisions. See Daniel L. Shaw, Sanket S. Dhruva & Joseph S. Ross, Coverage of Novel Therapeutic Agents by Medicare Prescription Drug Plans Following FDA Approval, 24 *J. Managed Care & Specialty Pharmacy* 1230, 1230–1231 (2018), <https://doi.org/10.18553/jmcp.2018.24.12.1230> (a Medicare Part D study finding variable and often restricted coverage after approval). Coverage decisions are made separately by Medicare and Medicaid authorities and private commercial payers. ↑
133. Trinity Life Sciences, U.S. Cell & Gene Therapy Access: Overcoming Barriers in 2025, <https://trinitylifesciences.com/blog/solving-the-cell-gene-therapy-access-puzzle-in-the-us/> (documenting Medicaid gaps, code- and rebate-file delays, and one commercial insurer’s 2025 policy to delay coverage of accelerated-approval products by 18 months). ↑
134. Lorlatinib (Lorbrena; Pfizer) was approved in Japan under the conditional early approval pathway. See Anju Murayama et al., Japan’s Conditional Early Approval Program for Innovative Cancer Drugs: Comparison of the Regulatory Processes with the US FDA and the EMA, 39 *Cancer Cell* 1165, 1165–1166 (2021), <https://doi.org/10.1016/j.ccell.2021.07.008> (lorlatinib among four CEA-approved oncology drugs; none had received full Japanese approval and none of the post-approval evaluations were complete as of June 2021). ↑
135. 42 U.S.C. § 262(i)(1); 21 C.F.R. § 600.3(h)(6), <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-600/subpart-A/section-600.3> (defining protein as an alpha amino acid polymer with a specific, defined sequence greater than forty amino acids in size). ↑
136. 21 U.S.C. § 353a (compounding with a bulk drug substance lacking a USP/NF monograph and not a component of an approved drug is permitted only if the substance appears on a list developed by the Secretary through notice-and-comment rulemaking); 21 C.F.R. § 216.23 (the codified § 503A bulk-substances list). On the unreviewability of an agency’s decision not to enforce, see *Heckler v. Chaney*, 470 U.S. 821 (1985). ↑

137. FDA, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act, <https://www.fda.gov/media/174456/download>; Bulk Drug Substances Nominated for Use in Compounding Under Section 503A, <https://www.fda.gov/drugs/human-drug-compounding/bulk-drug-substances-used-compounding-under-section-503a-fdc-act>. The Category 1/2/3 framework is a guidance statement of enforcement-discretion posture, not a legislative rule; only placement on 21 C.F.R. § 216.23 confers durable authorization to compound. ↑
138. FDA, Certain Bulk Drug Substances for Use in Compounding That May Present Significant Safety Risks, <https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks> (last visited Oct. 10, 2026); Press Release, EVEXIAS, Texas Healthcare Providers Lead Legal Challenge to FDA's Extralegal Prohibition of Peptide Therapies (Apr. 2, 2024), <https://peptidelegalfund.com/fda-peptide-lawsuit/> (plaintiffs' account of the September 2023 categorization). Complaint, Evexias Medical Centers, PLLC v. U.S. Food & Drug Administration, No. 4:24-cv-00293 (N.D. Tex. Mar. 29, 2024). The lawsuit challenged the categorization under the Administrative Procedure Act; April 2 is the press-release date, not the complaint date. FDA's 2024 committee materials address selected nominated substances, not the entire peptide roster: FDA, Pharmacy Compounding Advisory Committee, Oct. 29, 2024 Meeting Transcript, <https://www.fda.gov/media/185414/download>; FDA, Pharmacy Compounding Advisory Committee, Dec. 4, 2024 Briefing Document, <https://www.fda.gov/media/183583/download>, and Meeting Transcript, <https://www.fda.gov/media/185641/download> (including ipamorelin-related substances at the October meeting and CJC-1295, AOD-9604, and thymosin alpha-1-related substances at the December meeting). Advisory recommendations are distinct from final placement on the codified § 503A bulks list; removal from a guidance category alone does not authorize compounding. ↑
139. ISSCR Applauds New Japanese Rules Allowing Human-to-Animal Chimeric Embryo Research, Int'l Soc'y for Stem Cell Research (Mar. 13, 2019), <https://www.isscr.org/isscr-news/isscr-applauds-new-japanese-rules-allowing-human-to-animal-chimeric-embryo-research> (quoting ISSCR President Doug Melton: "Japan's new rules will enable a new generation of research that could potentially lead to the production of human organs for transplantation"); see Tsutomu Sawai et al., Japan Significantly Relaxes Its Human-Animal Chimeric Embryo Research Regulations, 24 Cell Stem Cell 513 (2019). ↑
140. NIH Guidelines for Human Stem Cell Research § V, <https://stemcells.nih.gov/research-policy/guidelines-for-human-stem-cell-research> (prohibiting NIH funding for the introduction of human pluripotent stem cells into non-human primate blastocysts and for breeding where such cells may contribute to the germline); Dickey-Wicker Amendment, e.g., Omnibus Appropriations Act, 2009, Pub. L. No. 111-8, § 509 (barring federal funding for the creation or destruction of human embryos for research). ↑
141. See Assisted Human Reproduction Act, S.C. 2004, c. 2, s. 5(1)(i)–(j) (Can.); Prohibition of Human Cloning for Reproduction Act 2002 (Cth) ss. 17–19 (Austl.) (s. 17: creating a chimeric embryo punishable by up to 15 years' imprisonment; s. 19(1): prohibiting placement of a human embryo in an animal); Embryonenschutzgesetz [Embryo Protection Act] § 7 (Ger.); Bundesverfassung [Federal Constitution] art. 119 (Switz.); Human Fertilisation and Embryology Act 1990, § 4A(4) (UK) ("A licence cannot authorise placing a human admixed embryo in an animal."). The United States has no analogous federal statute. ↑
142. *Dickey-Wicker Amendment*, 1996, Embryo Project Encyclopedia (Aug. 27, 2010), <https://embryo.asu.edu/pages/dickey-wicker-amendment-1996>. ↑
143. Carrie D. Wolinetz, A Quick Word About Human Embryo Model Systems, NIH Office of Science Policy (Oct. 10, 2019), <https://osp.od.nih.gov/a-quick-word-about-human-embryo-model-systems/> (describing case-by-case assessment of experimental details against NIH's statutory limitation on funding human-embryo research). ↑
144. See Hans-Werner Denker, Autonomy in the Development of Stem Cell-Derived Embryoids, 10 Cells 1461 (2021), <https://doi.org/10.3390/cells10061461>. ↑
145. NHMRC, Determining Whether an Embryo Model Is Regulated by the ERLC, <https://www.nhmrc.gov.au/research-policy/embryo-research-licensing/commonwealth-and-state-legislation/determining-whether-embryo-model-regulated-erlc>. ↑
146. The authors are grateful to Divya Dhar Cohen for this proposal. ↑

147. Carsten T. Charlesworth, Henry T. Greely & Hiromitsu Nakauchi, Opinion, *Ethically Sourced “Spare” Human Bodies Could Revolutionize Medicine*, MIT Tech. Rev. (Mar. 25, 2025), <https://www.technologyreview.com/2025/03/25/1113611/ethically-sourced-spare-human-bodies-could-revolutionize-medicine/>. ↑
148. Del. Code Ann. tit. 16, § 2710(4) (2024) (defining “anatomical gift” as “a donation of all or part of a human body to take effect after the donor’s death for the purpose of transplantation, therapy, research, or education”); see *id.* § 2712 (enumerating permissible purposes); *id.* § 2718 (short title, “Uniform Anatomical Gift Act”); see *generally* Unif. Anatomical Gift Act (Unif. L. Comm’n 2006). ↑
149. This statutory language is illustrative drafting; no jurisdiction has enacted a “bodyoid” provision or otherwise extended the Uniform Anatomical Gift Act to stem-cell-derived constructs. *Cf.* Del. Code Ann. tit. 16, § 2710 (2024) (definitions). ↑
150. Human Fertilisation & Embryology Authority, HFEA Comments on the News That Eight Babies Have Been Born After Mitochondrial Donation Treatment (July 2025), <https://www.hfea.gov.uk/about-us/news-and-press-releases/2025/hfea-comments-on-the-news-that-eight-babies-have-been-born-after-mitochondrial-donation-treatment/>; Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, SI 2015/572, <https://www.legislation.gov.uk/ukSI/2015/572/contents/made>. ↑
151. FDA, Advisory on Legal Restrictions on the Use of Mitochondrial Replacement Techniques to Introduce Donor Mitochondria into Reproductive Cells Intended for Transfer into a Human Recipient, <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/advisory-legal-restrictions-use-mitochondrial-replacement-techniques-introduce-donor-mitochondria> (last visited Oct. 10, 2026) (annual appropriations restrictions since December 2015 prevent FDA from accepting applications for clinical research using MRT). ↑
152. Memorandum from James M. Cole, Deputy Attorney General, to All United States Attorneys, Guidance Regarding Marijuana Enforcement 1–4 (Aug. 29, 2013), <https://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf>; Memorandum from Jefferson B. Sessions III, Attorney General, to All United States Attorneys, Marijuana Enforcement (Jan. 4, 2018), <https://www.justice.gov/opa/press-release/file/1022196/dl> (rescinding previous marijuana-specific guidance). ↑
153. Statement of Sen. Johnson of Wisconsin, 162 Cong. Rec. S6173 (daily ed. Sept. 28, 2016), <https://www.congress.gov/congressional-record/2016/09/28/senate-section/article/S6173-1>. ↑
154. Act of June 26, 2025, ch. 2025-185, §§ 1–2, 2025 Fla. Laws (codified at Fla. Stat. §§ 458.3245, 459.0127), <https://www.flsenate.gov/Session/Bill/2025/1768/BillText/er/HTML>. ↑
155. Fla. Bd. of Med., Minutes of the Stem Cell Therapy Workgroup (Jan. 8, 2026), https://www10.doh.state.fl.us/pub/medicine/Agenda_Info/Public_Information/Public_Minutes/2026/January/01082026_STEM_Minutes.pdf. ↑
156. Act of May 12, 2025, ch. 621, 2025 Mont. Laws (S.B. 535) (codified as amended in scattered sections of Mont. Code Ann. tit. 50, ch. 5 & 12), https://archive.legmt.gov/content/Sessions/69th/Contractor_index/CH0621.pdf. ↑
157. Ian Huyett, *HUYETT: An NH-Affiliated Company Growing Artificial Hearts Should Test Them in NH*, N.H. J. (Aug. 2, 2025), <https://nhjournal.com/huyett-an-nh-affiliated-company-growing-artificial-hearts-should-test-them-in-nh/>. ↑
158. N.H. Rev. Stat. Ann. § 126-Z:3 (2025), <https://gc.nh.gov/rsa/html/x/126-z/126-z-mrg.htm>. ↑
159. Granite Bio Innovation (@GraniteBio), X (June 4, 2026, 12:12 PM), <https://x.com/GraniteBio/status/2062568220393980386>. ↑
160. The same guidance power could address the challenge-trial problem. HHS or FDA could distinguish a pathogen administered solely to model infection from a therapeutic investigational product and consider a pathway centered on ethical review. The United Kingdom distinguishes infection-model studies, which receive no MHRA CTA and whose challenge agents receive no MHRA GMP certificate, from medicinal-product efficacy trials, which still require MHRA

authorization. See MHRA, COVID-19 Vaccines Benefit Risk Expert Working Group, Minutes of Oct. 28, 2020 Meeting, paras. 5.2–5.4, at 6, https://assets.publishing.service.gov.uk/media/67a51f080e720adbd4f6ae2c/28_October_2020.pdf. Reclassification could remove a regulatory obstacle, but would not by itself establish that US COVID-19 challenge trials would have proceeded. ↑

161. *Cf.* 21 C.F.R. § 314.510 (permitting approval on the basis of “adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit”); see *id.* § 314.500 (limiting the subpart to products “studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments”). ↑
162. Admin. Conf. of the U.S., Recommendation 91-9, Specialized Review of Administrative Action, 56 Fed. Reg. 67,143 (Dec. 30, 1991). ↑
163. See Harold H. Bruff, Specialized Courts in Administrative Law, 43 Admin. L. Rev. 329, 333 (1991). ↑